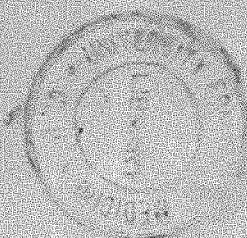


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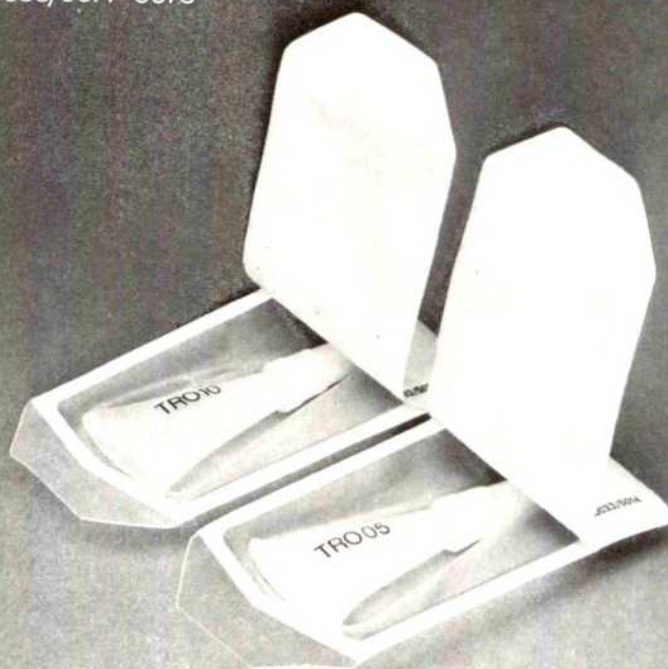
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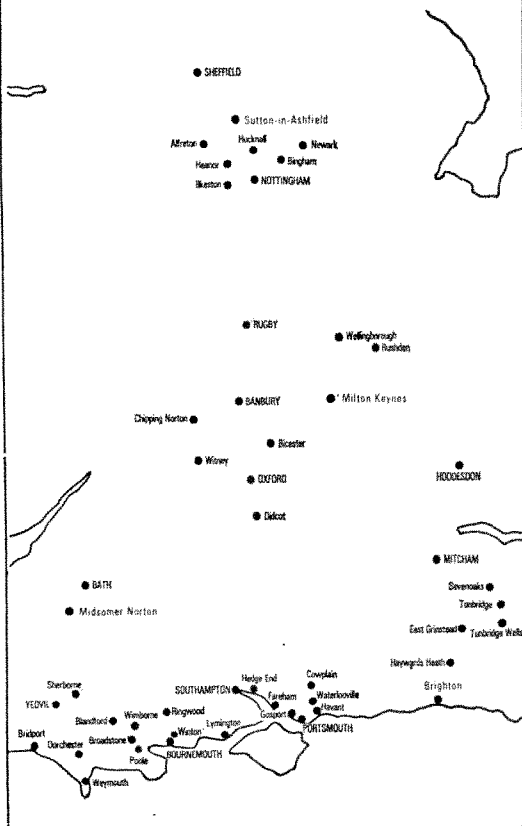
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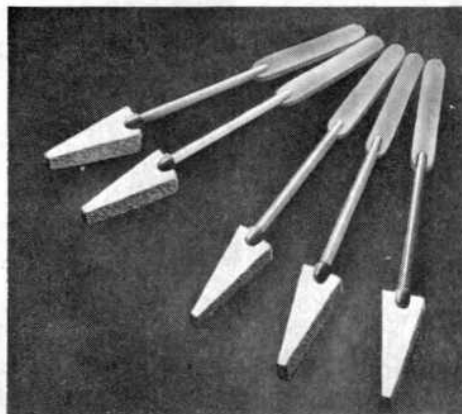


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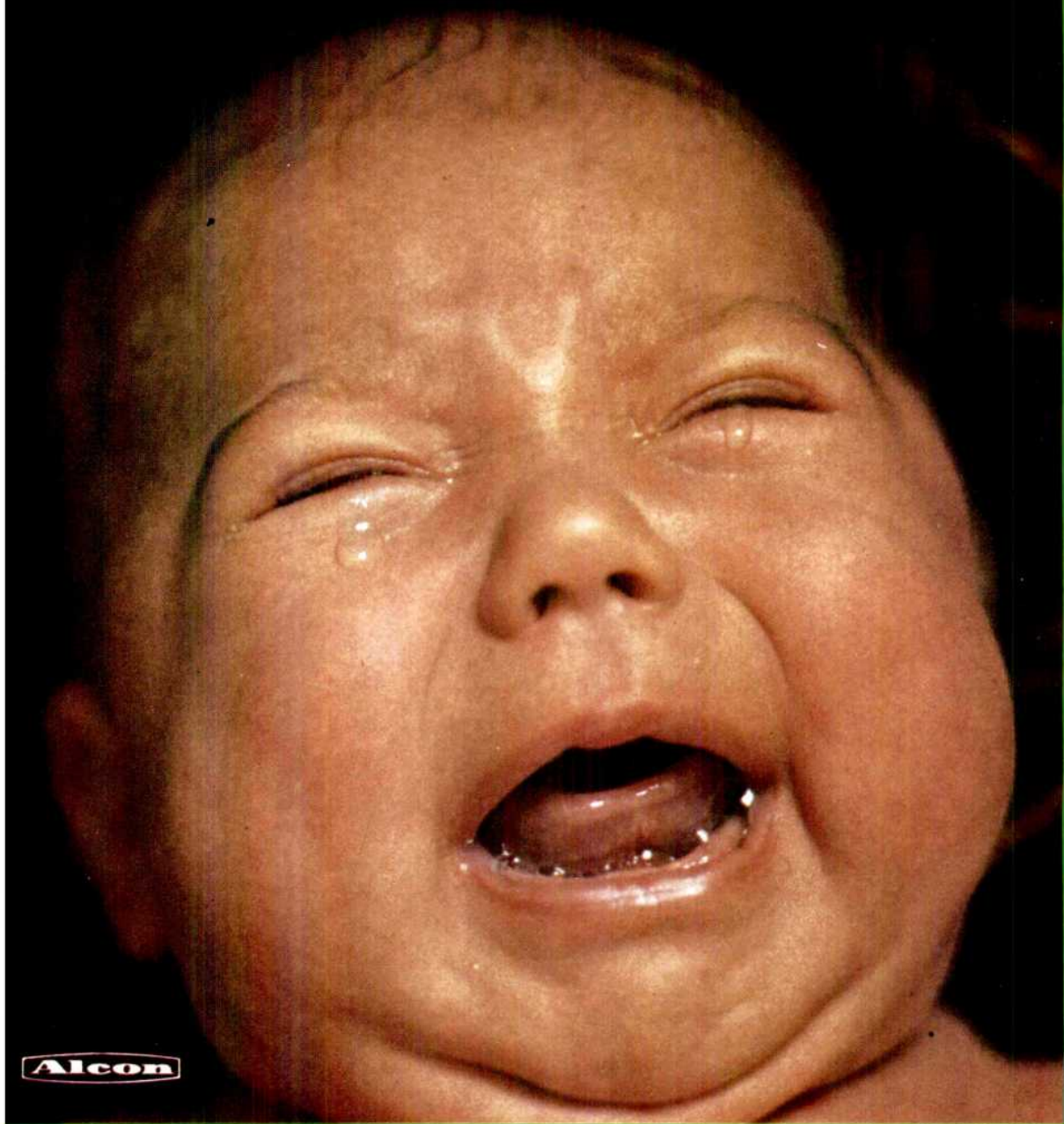
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Editorial: Congenital nystagmus .

In any disorder of ocular motility the ultimate aim in the persistent searching for knowledge about its fundamental nature is to try to secure some form of effective treatment. This has been achieved to a remarkable extent in many types of squint because of an increasing understanding of the underlying sensory and motor disorders, but it is evident that similar progress has not been made in the management of nystagmus. To a large extent this is because nystagmus is usually an expression of some visual, neurological, or vestibular disorder, so that treatment must be directed to the cause of the nystagmus rather than to the disorder of ocular motility. But this does not apply in congenital nystagmus of the so-called idiopathic type, when various direct methods of treatment are available.

Of course the prefix 'idiopathic' is unsatisfactory because it implies an ignorance of the mode of origin of congenital nystagmus, but it is reasonable to regard the causative lesion as lying in the complex nervous mechanisms in the brain stem which are concerned in the centring and in the so-called 'steady fixation' of the eyes. In this way the nystagmus may be regarded as an exaggeration of the fine persistent movements of the eyes (micro-saccades, slow motion random drifts, and rapid impulsive saccades which correct the random drifts) which are essential in the maintenance of a clear foveal perception of the retinal image.

Interest in the surgical treatment of nystagmus was generated by Anderson¹ and Kestenbaum,² and, although there are distinct differences in the 2 methods, the basic aim is to transfer the 'neutral point' (where the nystagmus is least evident) from an eccentric position to a straight-ahead position so that there is an elimination (or more usually a reduction) in the compensatory head posture. The surgical method consists essentially in moving both eyes so that they become 'straight' relative to the compensatory head posture.

Prismotherapy may be applied to achieve a similar effect, so that the eyes are maintained in the eccentric position (the 'neutral point') and yet regard the fixation object without any compensatory head posture. An entirely different form of prismotherapy may be attempted with a maintenance of the eyes in a position of marked convergence

(using base-out prisms) and yet fixing on a distant target, so that use is made of the so-called convergence block of the nystagmus.

The Fadenoperation put forward by Cüppers³ represents a different approach to the problem and is based on the concept that the necessary muscle force for any given ocular movement steadily increases after leaving the arc of contact of the globe. The operation consists in creating a second insertion of certain extrinsic ocular muscles (usually both medial recti) at least 10 mm behind the physiological insertion.

Various drugs have been tried (barbiturates, sodium diphenylhydantoin, coltramy, etc.), but these act simply by depressing nervous activity in general so that there is no specific effect on the nystagmus. Recently interest has been revived in the injection of botulism toxin into certain extrinsic ocular muscles to induce a temporary paresis in squint treatment,⁴ and perhaps it may prove to have some part to play in the management of congenital nystagmus.

An attempt has been made by a subjective method to achieve a stability of the nystagmus by the application of pleoptic methods.⁵ The patient attempts to superimpose the real image of an object (which is moving) and the after-image which is created in the central part of the retina (which is stationary), but this theoretical concept has not proved to be of practical value. It is interesting that a new subjective method has been put forward (page 2) in which the movements of the nystagmus are converted to audible stimuli so that they can be heard by the patient, and with this feedback signal an attempt is made to control the nystagmus by maintaining a constant tone. This represents a fascinating concept, but its efficacy particularly in children is not established yet.

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A new treatment for congenital nystagmus

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SUMMARY Congenital nystagmus is a disorder of eye movement with an associated reduction in visual acuity. The latter is mainly due to the intensity of the nystagmus (amplitude times frequency) allowing the object of regard to spend only a short time on the fovea. Training patients by an auditory feedback technique to control the nystagmus enables visual sensitivity to improve. This method is compared with present alternatives, and further studies are suggested.

Estimations of the incidence of congenital nystagmus (CN) in the general population vary enormously. The data of Hemmes (1926), 1 in 5000, Anderson (1953), 1 in 350, and Norn (1964), 1 in 20 000, provide a surprisingly large range, which most probably reflects not only the researchers' differing definitions of the condition but also the manner in which they collected the data. Perhaps a more clinically pertinent survey was that made by Fine (1968). She found that in England and Wales nystagmus was the fourth largest (11.2-14%) cause of partial sight.

In this study CN is defined as involuntary ocular oscillations occurring at birth or soon after (3 months), owing its origin to genetic, intrauterine, or birth influences. Characteristically, the dominant eye movements are bilateral and horizontal, although on occasion a vertical nystagmus, which usually signifies an acquired disorder, has been reported as being inherited (Forsythe, 1955; Marmor, 1973). The intensity (amplitude $\times$ frequency) of the nystagmus may vary enormously from individual to individual, and it may alter for each direction of gaze (Dell'Osso, 1973; Abadi and Sandikcioglu, 1974). Visual sensitivity for both pattern and movement detection is reduced because of these eye movements (Abadi, 1974a; Abadi and Sandikcioglu, 1975). This is understandable, since the object of regard spends little time in the foveal area, and the blur caused by the image movement, often in excess of 50°/s, is considerable (Abadi and Sandikcioglu, 1974; Dell'Osso and Daroff, 1975). In congenital nystagmus no oscillopsia (apparent movement of the environment) is noticed.

Accepting that the congenital nystagmat has a

major visual problem, how can the clinician remedy the situation? In the past a number of techniques, both optical and surgical, have been attempted, though none seem able to provide a suitable method for the diversity of cases encountered. Moreover, the specific nature of these therapies do not make them readily modifiable (see Discussion).

It is the aim, therefore, of this paper to report a new method which should provide an improvement in visual sensitivity for most individuals with CN. Simply, we proposed to let the subjects of our study hear their own eye movements and thereby attempt to use this feedback signal to control their nystagmus.

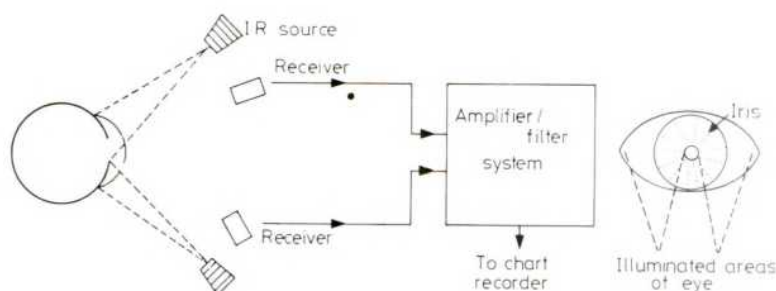
Methods

To be able to understand any eye movement disorder and monitor its improvement after therapy both the motor and sensory responses need to be examined. These include nystagmus intensity and the visual sensitivity.

RECORDING THE EYE MOVEMENTS

A modified photoelectric method was employed to monitor the nystagmus (Stark *et al.*, 1962). Infrared sources (TIL 24) and receivers (LS 614) were used to detect changes in limbal reflection due to the involuntary horizontal nystagmus (Fig. 1). These devices were mounted on a small printed circuit board and attached to the spectacles of the observer (Fig. 2). The reflected infrared light is detected by the receiver and fed into a preamplifier, the resultant amplified signal being then used to control the frequency of a voltage-controlled oscillator operating in the audiorange of 200-2000 Hz. The output of this oscillator, after amplification, is used to operate

Fig. 1 The infrared source and photocell receiver arrangement for recording eye movements



a small loudspeaker. Thus the subject can hear a tone, the frequency of which is altered by the eye movements.

Using this feedback device we have attempted to control the degree of nystagmus by asking the subjects to try to keep the tone constant. In order to assess the degree of success of this technique we monitored the intensity and velocity of the nystagmus, before, during, and after the course of training.

MEASURING CONTRAST THRESHOLDS

At all stages of training, psychophysical contrast sensitivity functions were measured to give an indication of improved visual sensitivity. Both vertical and horizontal sinusoidal grating patterns were generated on the face of a Telequipment D61 oscilloscope (P31 phosphor), and each observer was asked to find his own contrast threshold at different spatial frequencies by adjusting a potentiometer which altered the contrast of the patterns (Schade, 1956; Campbell and Green, 1965; Abadi, 1974b; Arden, 1978). The contrast of the grating pattern is defined as the ratio of the difference of the maximum and minimum luminance over their sum. Contrast sensitivity is the inverse of contrast threshold, and spatial frequency is an equivalent measure of bar size in a grating pattern; that is, it is the number of alternating pairs of dark and

bright bands of the pattern subtended in degrees of visual angle at the observer's eye. The mean screen luminance was constant at 7 cd/m^2 , subtending an angle of 8° when the viewing distance was 57 cm. Monocular viewing of the circular display was used throughout, and all subjects were fully corrected for any refractive errors.

SUBJECTS

Although we have now 'trained' a number of subjects to use the equipment, this paper will detail the typically favourable results achieved by describing the data of one such observer, a 22-year-old male. After trial runs in the laboratory he took the feedback equipment home and over a period of 24 weeks practised keeping the tone constant for 5–10 minutes each morning and evening.

Results

Contrast sensitivity functions for prefeedback and postfeedback are illustrated in Figs. 3a and b. The visual sensitivity to horizontal patterns is seen to be greater than that for vertical ones and confirms the earlier studies of Abadi (1974a) and Abadi and Sandikcioglu (1975). This effect is caused by the horizontal motion of the nystagmus and is not due to any uncorrected refractive error or meridional amblyopia from an uncorrected astigmatism acquired early in life. Indeed it has recently been demonstrated by Abadi and King-Smith (in press) that if the eye movements are eliminated the orientational sensitivity bias is still present, suggesting that the oculomotor disturbance may be responsible for depriving the cortical orientational detectors of a normal visual input and thus giving rise to a meridional amblyopia.

After feedback training visual sensitivity for both meridians is shown to have improved. Moreover the intensity of the nystagmus has been reduced from an initial level of $3.59^\circ \pm 0.36^\circ / 4.75 \text{ Hz} \pm 0.33 \text{ Hz}$ to $2.64^\circ \pm 0.29^\circ / 3.88 \text{ Hz} \pm 0.28 \text{ Hz}$ (Fig. 3, insets). In terms of the velocity of the image moving in the back of the retina this would consti-



Fig. 2 Subject using the eye movement recording spectacles and listening for a change in tone from the speaker

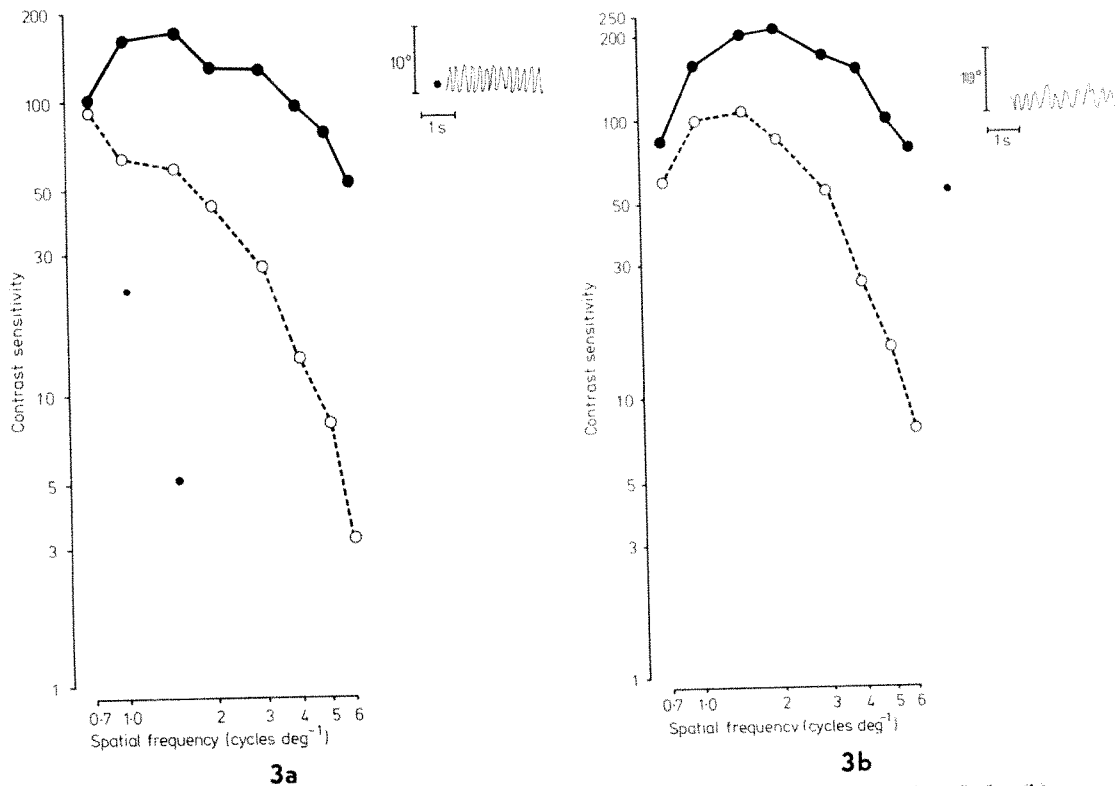


Fig. 3 Spatial contrast sensitivity functions for an observer with congenital nystagmus before (a) and after (b) auditory feedback training. The filled and empty symbols refer to thresholds (mean of 20) in response to horizontally and vertically orientated patterns respectively. Insets illustrate the form and intensity of the nystagmus

tute an approximate reduction from a value of 54°/s to 32°/s. Consequently the image, which is now less blurred, also spends more time on the fovea. Fig. 4 shows the postfeedback to prefeedback contrast sensitivity ratios for viewing a horizontal grating pattern (top) and a vertical pattern (bottom), indicating sensitivity improvements of 0.17 ($\times 1.5$) and 0.30 ($\times 2.0$) log units respectively. This change was maintained after training had ceased.

In our studies the subjects were adults and showed feedback changes of between 0.13 to 0.32 log units.

Discussion

Using a biofeedback technique we are able to report that after training it is possible to improve the visual sensitivity and hence the visual resolution of adults with CN. Indeed this 'learned self-control' is also illustrated by a reduction in both the amplitude and frequency of the nystagmus (Fig. 3,

insets). Of course, this does not mean that the familiar methods of management of nystagmus, namely, optical and surgical, will be replaced. Rather the training routine could augment these more traditional and specific therapies. Consequently it would not be out of order briefly to consider them here and reflect on their limitations.

TRADITIONAL MANAGEMENT OF NYSTAGMUS

Optical treatment. Contact lenses have been used as an optical aid. Their advantages for patients with albinism or aniridia can be immense (Enoch and Hudson, 1968), because the incident light entering the eye can be more easily controlled. Claims have also been made that the superiority of the optical system of a contact lens over a spectacle lens can be an important factor in improving vision (Grosvenor, 1963). From an optical point of view the contact lens correction should provide fewer distortions and aberrations, and the prismatic displacements which occur with spectacle lenses

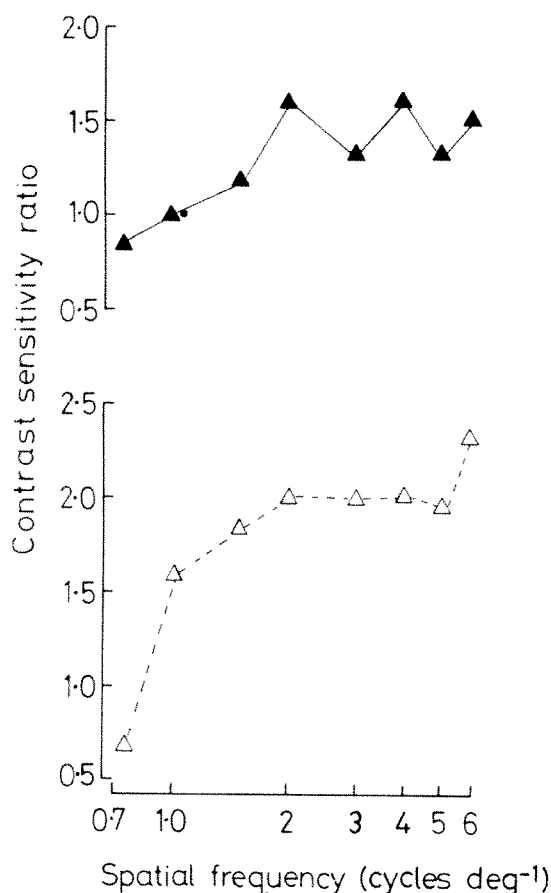


Fig. 4 Contrast sensitivity ratios comparing prefeedback with postfeedback data. The upper graph illustrates the postfeedback/prefeedback ratio for horizontal stimuli, and the lower graph shows the equivalent ratio for vertical stimuli

because of the moving eye are much reduced with the contact lens systems.

Quite often the amplitude and frequency of CN varies with positions of gaze, and in one direction, the neutral zone, the nystagmus intensity can be greatly reduced (Kestenbaum, 1953; Dell'Osso, 1973; Abadi and Sandikcioglu, 1974). The use of prisms to direct the eyes to this position has been attempted by Dell'Osso *et al.* (1972). With convergence providing the stimulus for an attenuation on the nystagmus intensity (Abadi and Sandikcioglu, 1974) base-out prisms have been used to induce this vergence (Metzger, 1950).

Surgical treatment. To place the neutral zone in the primary position of gaze a patient may take up a compensatory head posture. To prevent this torticollis surgical techniques are available to direct the

eyes to coincide with this position. Two types of operations may be carried out. The first entails the relocation of the eyes by operating on all 4 horizontal recti (Anderson, 1953; Kestenbaum, 1953). The second, a more drastic approach, entails immobilisation, either by fixing the ocular muscles to the periosteum (Friede, 1956) or by the less extreme retroequatorial recession method (Bietti, 1956; Crone, 1971).

AUDITORY FEEDBACK

The techniques just described are specialised solutions to particular aspects of CN and do not offer a general solution that is both practical and simple. For example, prism therapy relies on the existence of a marked neutral point. Alternatively, by using base in prisms it can present after short periods of time symptoms typical of eye strain (Wybar, 1974). Surgery is primarily attempted to counter torticollis and is complicated if a strabismus is also present. Moreover it is appropriate only if the nystagmus is jerky (both fast and slow phases). On the other hand, biofeedback offers the subject a self-trainer to be used either by itself or in conjunction with other optical or surgical methods.

Although the reported improvements in visual sensitivity never reached levels greater than 0.32 log units, it may be argued that the visual system is far from plastic in adults (Barlow, 1975). A study is therefore now in progress to find the effects of the same training schedule on young children where the visual system is known to be more adaptable.

As a further use, this auditory signal technique can be extended to detecting and correcting other oculomotor deviations, for example, squints, and be used to train accurate fixation in individuals with amblyopia.

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Increased drift in amblyopic eyes

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ABSTRACT Reports are conflicting on the presence of increased drift in amblyopic eyes. Furthermore, the individual effects of either amblyopia or strabismus alone on ocular drift have not been systematically investigated. We therefore used a photoelectric method to record horizontal eye position during monocular and binocular fixation in patients having amblyopia without strabismus, intermittent strabismus, or constant strabismus amblyopia. Our principal finding was increased drift amplitude (up to 3.5 degrees) and velocity (up to 3.0 degrees per second) in amblyopic eyes during monocular fixation. While increased drift was found 75% of the time in amblyopia without strabismus and 50% of the time in constant strabismus amblyopia, it was found only 20% of the time in intermittent strabismus. Amblyopic drift could be either error-producing or error-correcting in nature. Increased drift was not present during monocular fixation with the dominant eye or during binocular fixation in any of our 16 patients. We therefore conclude that amblyopia and not strabismus is a necessary condition for the presence of markedly increased fixational drift. Increased drift amplitude but not velocity may adversely affect visual acuity in the amblyopic eye.

The eye is not perfectly still during attempted steady fixation. Fine high-frequency tremor, microsaccades, and slow drifts keep the eye in constant motion, and these phenomena have been quantitatively analysed in detail in normal subjects (Ditchburn, 1974).

Fixational eye movements in persons with amblyopia and strabismus have also been studied, though whether they have increased ocular drift remains unclear. Matteucci (1960) presented records showing the fixation pattern in 1 patient having amblyopia without strabismus and several patients having strabismus amblyopia. Pronounced drift appeared to be present in all records, but it was not quantified. Lawwill (1968) observed, but did not record, horizontal drifts as large as 2 degrees in amplitude in the amblyopic eyes of strabismic amblyopes during monocular fixation. Accurate fixation was shorter and drift magnitudes greater in patients with deep amblyopia. In contrast Schor and Flom (1975) found similar drift magnitude, duration, velocity, and direction between the amblyopic eye and fellow dominant eye in patients with constant strabismus amblyopia. However, recently Schor and Hallmark (1978) reported increased mean drift velocities in the amblyopic eye of some patients with

strabismus amblyopia, but their method of analysis was not specified, and mean drift amplitudes were not provided.

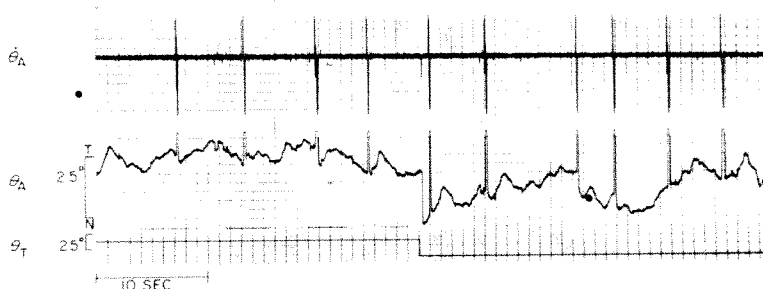
Thus reports are conflicting and incomplete on the presence of increased drift amplitude and velocity in amblyopic eyes. Furthermore, most patients in previous studies had both amblyopia and strabismus. The individual effects of either amblyopia or strabismus alone on ocular drift have not been systematically investigated. Therefore in our study we expanded the test categories and quantitatively assessed fixational drift in patients having amblyopia without strabismus, intermittent strabismus, or constant strabismus amblyopia. Our results indicate that amblyopia and not strabismus appears to be a necessary condition for the presence of markedly increased drift.

Patients and methods

A photoelectric method was used to record horizontal eye position (Stark *et al.*, 1962). The band width of the entire recording system was 75 Hz (-3dB). Resolution was approximately 12 min arc. A chin rest and head rest, usually in conjunction with a bite bar covered with dental impression material, were used to stabilise the head. A PDP 8/I minicomputer was used to generate a small (3.5-5.0 min arc) bright test spot on a display screen placed either 57 or 91 cm in front of the

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Fig. 1 Monocular fixation with amblyopic eye. Patient 9, amblyopia without strabismus, 20/40. From top to bottom, eye velocity, eye position, and stimulus, respectively. Note increased drift amplitudes and velocities, and paucity of saccades comparable in magnitude to drifts. Deflections driving pens to edge of record due to blinks. Symbols for Figs. 1-4: N =nasalward eye movement, T =temporalward eye movement, θ_T =target position, θ_N =eye position normal eye, θ_{ND} =eye position non-dominant eye, θ_A =eye position amblyopic eye, and $\dot{\theta}_A$ =velocity amblyopic eye



subject on the midline. Target luminance was always maintained at least 1 log unit above screen luminance. Eye movements were recorded as the patients either monocularly or binocularly fixated a target positioned on the midline or 2.5 or 5.0 degrees to the left or right of midline for 15-60 seconds.

Patients were obtained from the clinics at the School of Optometry. All had a thorough visual examination and were free of ocular or neurological disease. Their ages ranged from 15 to 42 years, mean 26.8 years. The patients had amblyopia without strabismus, intermittent strabismus, or constant strabismus amblyopia. Spectacles or contact lenses were worn during all testing. See Table 1 for clinical data on each patient.

Drift was analysed directly from strip chart records for 15-30 consecutive seconds of midline fixation. Drift amplitude was determined in two ways: (1) the maximum peak to peak drift amplitude, regardless of time required for completion of the movement, was found; and (2) maximum peak to peak drift amplitude during consecutive 1 second fixation intervals was obtained and averaged. Drift velocity was also determined in two ways: (1) maximum drift velocity, regardless of time required for completion of the movement, was obtained; and (2) maximum drift velocity during a 200 ms period for consecutive 1 second intervals was obtained and averaged.

Results

The principal finding of our investigation was increased drift amplitude (>12 min arc) and velocity (>20 min arc/s) in amblyopic eyes during monocular fixation. Increased drift occurred most frequently and with greatest magnitude in amblyopia without strabismus and in constant strabismus (exotropia) amblyopia, while it occurred least frequently and with smallest magnitude in inter-

mittent strabismus. Increased drift was not present during binocular fixation or monocular fixation with the dominant eye in any patient. Drift characteristics of each patient were similar for all 5 horizontal directions of fixated gaze tested.

The presence of increased amblyopic drift is clearly seen in the eye movement records (Figs. 1-4). In patient 9 (Fig. 1, amblyopia without strabismus), increased drift amplitude (up to 3.3 degrees) with a paucity of comparably sized saccades, as well as increased drift velocity (up to 1.7 degrees per second), was prominent throughout the record. Drifts rather than saccades appeared to be used to attempt to maintain eye position during fixation. Thus, drifts functioned in either error-producing or error-correcting capacities. Comparison of monocular fixation in the amblyopic eye with monocular fixation in the fellow dominant eye is shown in Fig. 2 (patient 9, amblyopia without strabismus). The contrast between the extreme steadiness of the dominant eye (<12 min arc amplitude, <20 min arc/s velocity) and the increased drift in the amblyopic eye (1.8 degrees peak to peak amplitude and 1.7 degrees/second maximum velocity) is striking.

Important information on the cause of the drift can be ascertained from recordings of binocular eye movement during monocular fixation with the amblyopic eye. Fig. 3 represents such a record in patient 5 (constant strabismus amblyopia). This record clearly shows that the large, slow movement in the amblyopic eye is drift and is not due solely to accommodative vergence, since the movement is largest in the viewing eye (Kenyon *et al.*, 1978); it is not due solely to smooth pursuit, since the movements are nonconjugate; and finally it is not due to disparity (fusional) vergence, since the movements are not symmetrical, and they occur with 1 eye occluded.

Comparison of overall fixation patterns in each diagnostic group is of particular interest (Fig. 4). Patient 10 (Fig. 4, top), having amblyopia without

Table 1 Clinical data of patients

Patient	Age	Prescription	Visual acuity	Vergence abnormality (prism dioptres)	Eccentric fixation (prism dioptres)
<i>Constant strabismus amblyopia</i>					
1*	25	LE +2.00 = -0.25 × 130 RE +2.25	20/25 20/15	1-2 ET LE	1/2 nasal LE
2*	23	LE +3.75 = -0.50 × 165 RE -0.50	20/30 20/15	18 ET LE	1 nasal LE
3	15	LE -1.50 RE -1.75	20/122 20/20	10 ET LE and 1 HT LE	2.5 nasal and 2 superior LE
4	32	LE +4.00 RE plano	20/277 20/20	4 ET LE	16 nasal and 4 superior LE
5*	33	LE +0.75 = -0.50 × 40 RE +0.25 = -0.50 × 180	20/630 20/10	5-6 ET LE and 2 HT LE	2.5-3.5 nasal and 3-4 superior LE
6	29	LE -1.50 = -1.75 × 180 RE +4.00 = -1.50 × 180	20/15 20/137	4 XT RE and 2 HT RE	Unsteady central RE
7	42	LE -1.50 = -0.25 × 180 RE +1.00 = -0.50 × 15	20/20 20/200	20 XT RE	2 temporal RE
<i>Amblyopia without strabismus</i>					
8	24	LE +0.75 = -2.00 × 90 RE pl = -0.50 × 19	20/38 20/20	None	2 nasal and 2 inferior LE
9	25	LE -2.50 = -1.25 × 172 RE -5.00 = -0.75 × 5	20/25 20/40	None	2 nasal and 2 inferior RE
10**	19	LE +5.00 RE +3.00	20/110 20/15	None	2 temporal LE
11**	26	LE -0.25 RE -2.75 = -3.75 × 20	20/15 20/165	None	1 superior RE
<i>Intermittent strabismus with or without mild amblyopia</i>					
12	25	LE +0.25 RE -0.50	20/15 20/15	20 ALT. XT	Central, steady LE, RE
13	22	LE -0.75 = -0.25 × 148 RE -3.00 = -0.25 × 100	20/20 20/20	18 ALT. XT and 12 HT LE	Slight unsteady Central LE, RE
14*	31	LE -5.00 RE -4.50 = -0.75 × 20	20/20 20/20	15 XT LE	Central steady LE, RE
15**	32	LE +0.75 = -1.75 × 180 RE +1.25 = -3.50 × 5	20/20 20/23	40-50 XT RE	1 nasal and Superior RE
16	25	LE plano RE -1.00	20/32 20/16	10 XT LE and 20 HT LE	1/2 nasal LE

*Patients 1, 2, 5, and 14 had corrective eye muscle surgery. **Patients 10 and 15 began amblyopia therapy 1 year and 1 month before participating in our study, respectively, while patient 11 underwent a brief period of unsuccessful occlusion therapy at age 10.

strabismus, showed increased drift (up to 3.4 degrees amplitude and 1.5 degrees/second velocity) in the amblyopic eye. Fixational saccades comparable in magnitude to the drifts were rarely observed. Other patients in this diagnostic group showed similar drift characteristics (Figs. 5-7).

Patient 5 (Fig. 4, middle), having constant strabismus with deep amblyopia, frequently showed both increased drift (up to 3.5 degrees amplitude and 2.0 degrees/second velocity) and large saccades (up to 3.0 degrees amplitude) during fixation. Similar fixation characteristics were found for other patients

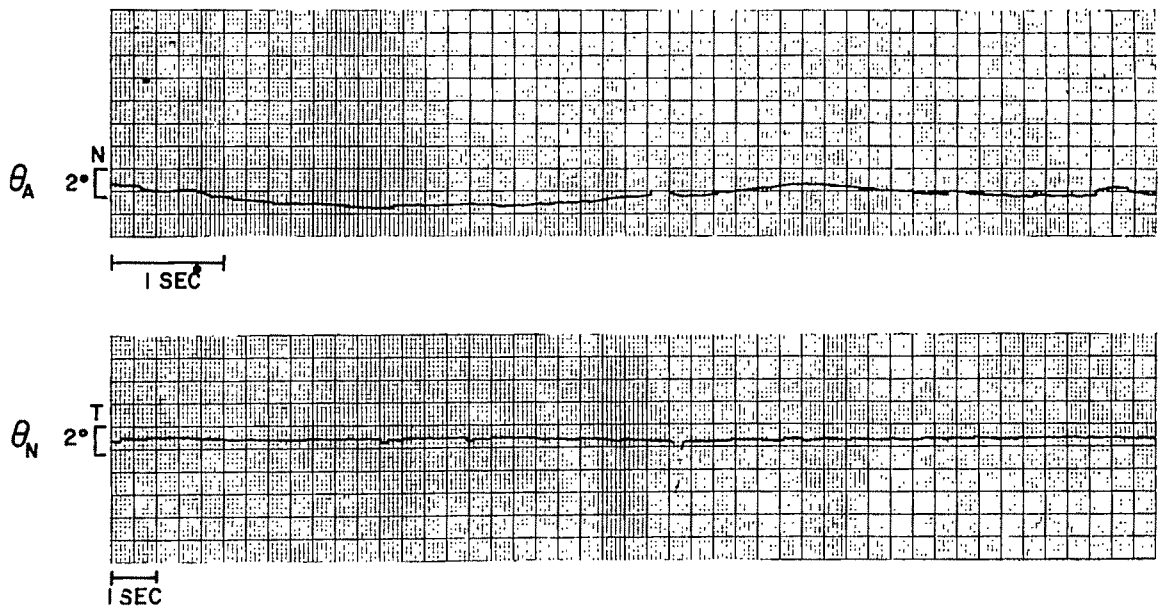


Fig. 2 Monocular fixation with amblyopic eye (top) and dominant eye (bottom). Patient 9, amblyopia without strabismus, 20/40. Prominent drift of amblyopic eye is in marked contrast to steadiness of dominant eye

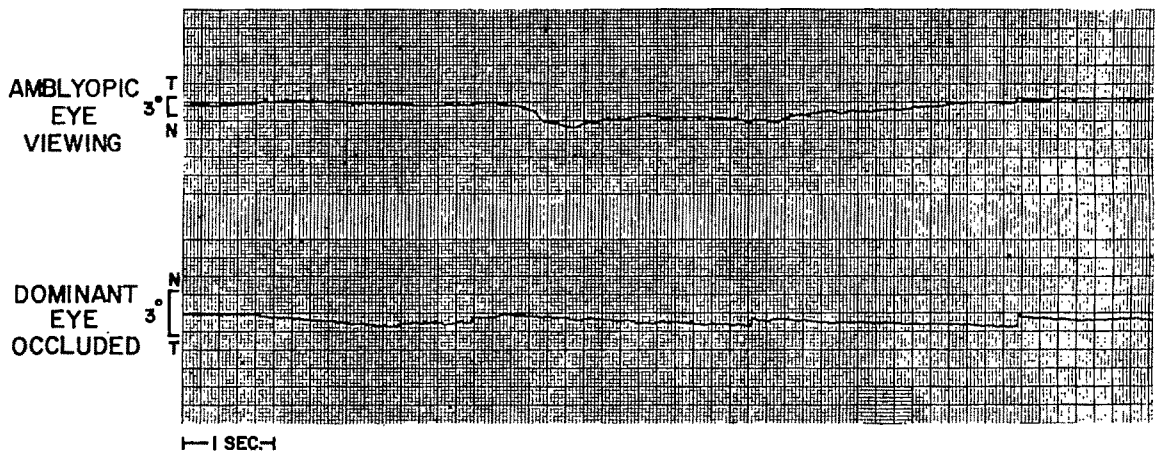


Fig. 3 Binocular eye movement recording during monocular fixation with amblyopic eye. Patient 5, constant strabismus amblyopia, 20/630. Small drifts (≤ 1.0 degree) in occluded dominant eye uncorrelated to movements in viewing amblyopic eye. Note large (about 3.5 degrees) nasalward drift in viewing amblyopic eye with only small drift in occluded dominant eye. Record clearly shows that this large, slow movement in the amblyopic eye is drift and is not due solely to accommodative vergence, nor to smooth pursuit alone, nor to disparity vergence

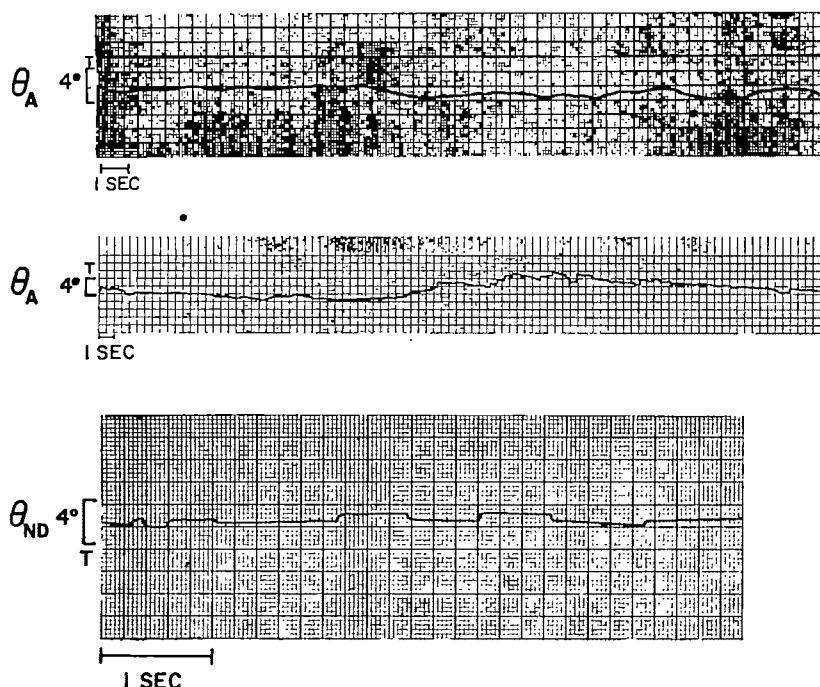


Fig. 4 Monocular fixation with amblyopic (or nondominant) eye in amblyopia without strabismus (patient 10), constant strabismus amblyopia (patient 5), and intermittent strabismus without amblyopia (patient 13), top to bottom, respectively. Note transition in overall general fixation pattern from predominantly drift (top) to drift and saccades (middle) to predominantly saccades (bottom)

in this diagnostic group (Figs. 5–7). For patient 13 (Fig. 4, bottom) having intermittent strabismus and normal acuity, saccadic intrusions (0.5–1.0 degree amplitudes) rather than significantly increased drifts were prominent during fixation, and this was true for most patients in this diagnostic group (Figs. 5–7). Thus, these results clearly show that the occurrence of markedly increased drift depended on the presence of amblyopia and not strabismus. The presence of strabismus alone resulted in normal or nearly normal drift characteristics, with large saccades (saccadic intrusions) now becoming the prominent feature of the fixation pattern (Ciuffreda *et al.*, 1979b).

A further analysis of drift is warranted. The presence of abnormal drift (the number of 1 second intervals in which increased drift amplitude or velocity was found divided by the total number of seconds fixation was tested times 100) was calculated for each patient (Fig. 5). Increased drift amplitude was found 50% of the time in constant strabismus amblyopia, occurring 34% of the time in the esotropes while increasing to 90% of the time in the exotropes. Increased drift velocity was found 56% of the time in constant strabismus amblyopia, occurring 43% of the time in the esotropes while increasing to 87% of the time in the exotropes. In amblyopia without strabismus increased drift amplitude and velocity occurred 67

and 85% of the time, respectively. Increased drift amplitude was found 13% of the time in intermittent strabismus, occurring only 8% of the time in patients with 20/20 or better visual acuity while increasing to 20% of the time in patients with worse than 20/20 visual acuity. Increased drift velocity was found 30% of the time in intermittent strabismus, occurring only 23% of the time in patients with 20/20 or better visual acuity while increasing to 40% of the time in patients with worse than 20/20 visual acuity. In constant strabismus (esotropia) amblyopia average maximum drift amplitude correlated well ($r_s = 0.975$, $P < 0.05$) with visual acuity of the amblyopic eye. Maximum peak to peak drift amplitude ($r_s = 0.90$, $P < 0.05$), and the presence of abnormal drift amplitude ($r_s = 0.90$, $P < 0.05$) also correlated well with visual acuity of the amblyopic eye in these 5 esotropic patients. In our 4 patients having amblyopia without strabismus there was a strong trend ($r_s = 0.95$, $P > 0.05$) for average maximum drift amplitude and velocity to correlate well with visual acuity of the amblyopic eye. No other significant correlations or strong trends were found.

Discussion

Increased drift was found in the amblyopic eyes of most of our patients. The increased drift amplitude

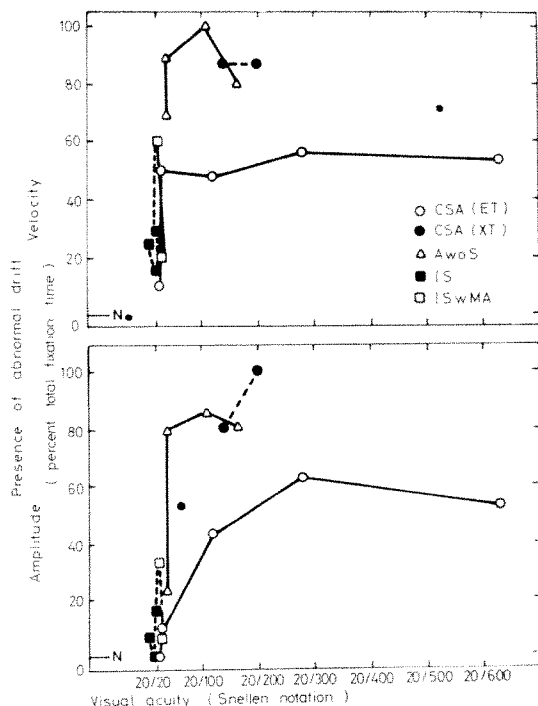


Fig. 5 Presence of abnormal drift (per cent total fixation time of increased drift) amplitude and velocity as a function of visual acuity in the nondominant eye. Symbols for figures 5-7: CSA(ET)=constant strabismus amblyopia (esotropia), CSA(XT)=constant strabismus amblyopia (exotropia), AwoS=amblyopia without strabismus, IS=intermittent strabismus with visual acuity of 20/20 or better, ISwMA=intermittent strabismus with mild amblyopia (visual acuity worse than 20/20), and N=maximum normal drift level during binocular fixation or monocular fixation with the dominant eye

and velocity were most pronounced in amblyopia without strabismus and constant strabismus (exotropia) amblyopia. It was evident to a lesser degree in constant strabismus (esotropia) amblyopia. Drift was either normal or nearly normal in the non-dominant eyes of most patients having intermittent strabismus. Thus, the results suggest that amblyopia and not strabismus was a necessary condition for the presence of significantly increased drift.

The slightly increased drift found in intermittent strabismus is of interest. Increased drift in this diagnostic group was most pronounced in patient 15. This was probably due to the presence of slightly reduced visual acuity and eccentric fixation in the eye. Further, the patient was undergoing active orthoptic treatment at this time, which may result in increased drift due to disruption of a

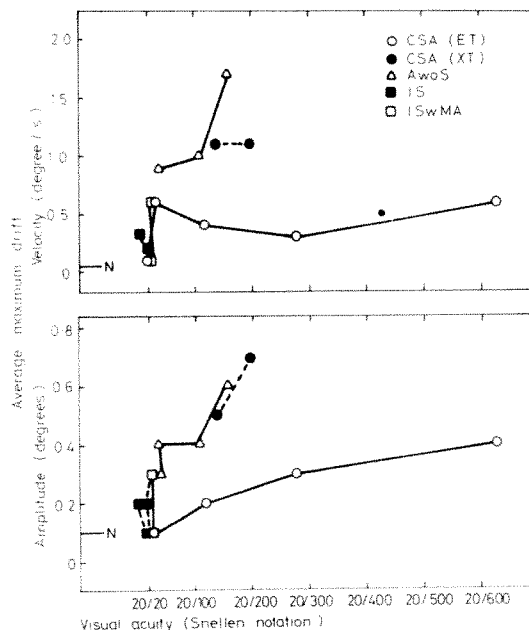


Fig. 6 Average maximum drift amplitude and velocity as a function of visual acuity in the nondominant eye

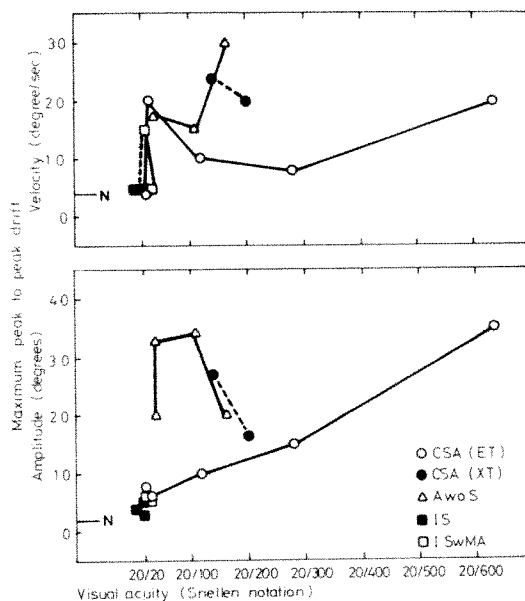


Fig. 7 Maximum peak to peak drift amplitude and velocity as a function of visual acuity in the nondominant eye

relatively fixed pattern of eccentric fixation in spite of concomitant improvement of visual acuity (Ciuffreda *et al.*, 1979a). The other patients in this group exhibited normal or nearly normal drift. Strabismus-induced fixation degradation, resulting in abnormally-large fixational saccades (saccadic intrusions) in most intermittent strabismics (Ciuffreda *et al.*, 1979b), could also account for part of this mild drift abnormality.

Increased drift amplitudes, without the occurrence of comparably sized corrective saccades (as was most dramatically found in patients having amblyopia without strabismus) suggest that drifts rather than saccades played a major role in the correction of fixation errors and in the maintenance of eye position in amblyopic eyes. Thus, drift could be either error-producing or error-correcting (Nachmias, 1959; St Cyr and Fender, 1968; Stark, 1971) in nature. It is interesting that Nachmias (1959), in analysing 2-dimensional monocular fixation eye movement records in normal subjects, found correction of position error by drifts in those meridians in which microsaccadic corrections appeared to be ineffective. If this line of reasoning is applied to our patients, it suggests that the micro-saccadic system, one of whose functions is to correct for drift-induced fixation errors, may be less effective in amblyopic eyes. Ineffectiveness of the micro-saccadic system may involve failure to integrate eye velocity (drift velocity) into a position error for subsequent correction by the saccadic system and/or processing delays in initiation of appropriately sized microsaccades, similar to the processing delays found for larger tracking saccades in amblyopic eyes (Ciuffreda *et al.*, 1978a, b). Increased drift amplitudes might also be found if processing delays in the smooth pursuit velocity-correcting system were present. These hypotheses regarding possible mechanisms underlying increased amblyopic drift amplitude warrant further careful experimental testing.

Could part of the increased drift amplitudes observed in amblyopic eyes be due to normal drift characteristics of the oculomotor system for position errors generated in the retinal periphery? Results of Sansbury *et al.* (1973) support this idea. In their experienced normal subjects, as error signals were generated by more peripheral retinal regions, small increases (a few minutes of arc) in drift magnitude were found. Thus it seems reasonable to attribute a small part of the increased drift amplitudes observed in our untrained amblyopic patients to this factor, since they did fixate on the average with nonfoveal regions, that is, eccentric fixation was present. The total extent over which the target image was displaced without execution of appropriate corrective movements may represent that region of the retina

most adversely affected, in terms of eye position maintenance, by amblyopia.

Drift velocities as high as 3.0 degrees per second were found in amblyopic eyes. If drift rates were similar between the normal and amblyopic eye, and only increased drift magnitudes were found in amblyopic eyes, this might point to a simple sensory basis for the abnormality in terms of defective sensing of position error over affected (by amblyopia) retinal regions, thus allowing the eye to drift for a longer period of time, but with normal drift velocities, until the target image extended out of this relatively insensitive area. At that time a position error would be sensed and a corrective movement initiated. That this might occur at times in amblyopic eyes has been discussed elsewhere (Ciuffreda, 1977). More frequently, however, increased drift velocities were observed which may either be a consequence of delays resulting from amblyopia in the smooth pursuit velocity-correcting system, thereby allowing long duration drifts with high velocities to evolve, or may in part simply result from fixation with non-foveal retinal regions.

What effect would increased drift have on visual acuity in amblyopic eyes? It has been clearly shown that retinal-image motion across the horizontal meridian of the fovea in normal persons must exceed 2.5 degrees per second before visual resolution is degraded (Westheimer and McKee, 1975). If this result is applied to the amblyopic eyes, visual acuity should be little if at all affected by the increased drift velocities (generally <2.5 degrees/second). However, increased drift amplitudes moving the retinal image on to more eccentric positions would reduce acuity, as shown by recent measures of the visual acuity gradient in the horizontal meridian in amblyopic eyes (Kirschen and Flom, 1978), while increased drift amplitudes in any direction would contribute to increased variability in the acuity measure.

The results showed that only certain parameters of drift correlated highly with visual acuity in the amblyopic eye (there were too few patients with constant exotropia and amblyopia to perform a statistical analysis, and in intermittent strabismus the range of acuities was too narrow). But should one necessarily expect a close relationship between *all* aspects of drift and visual acuity in the amblyopic eye? Other factors, such as age of onset of strabismus, constancy of the deviation, and age of initial correction of refractive error may influence degree of fixation control in the amblyopic eye. From our data, there was also a suggestion that direction of deviation may influence amblyopic drift characteristics. Our 2 patients with constant exotropia and amblyopia consistently had high drift values when

compared to our patients having constant esotropia with similar acuity losses. Further testing of patients with constant exotropia must be conducted before the idea that amblyopia secondary to exotropia is more detrimental to fixation control than amblyopia secondary to esotropia can gain support. Lastly, oculomotor control may be differently influenced by effects due primarily to suppression, as commonly found in strabismus with approximately equal refractive error, and those effects due primarily to mild form deprivation, as found in anisometropia.

The results of this study can provide insight into the clinical assessment of fixation in amblyopic eyes. During the visusopic examination the clinician estimates, with aid of a calibrated grid pattern projected on to the fundus, the magnitude (time-average position of the eye) and range (maximum peak to peak drift amplitude with microsaccadic amplitude superimposed) of eccentric fixation, as well as 'steadiness' of fixation—a judgment based on some unknown combination of average and maximum drift amplitude and velocity with microsaccadic amplitude superimposed. The presence of abnormal drift (in terms of per cent total fixation time) is difficult to quantify accurately, and the absolute value of average or maximum drift velocity is impossible to ascertain. Recent findings obtained with an objective eye movement recording technique show, for example, that average maximum drift amplitude and velocity tend to become normal during orthoptic treatment (Ciuffreda *et al.*, 1979a). These authors' results suggest that it is important to quantify accurately and completely these measures of drift during treatment, and a visusopic analysis alone is inadequate for such purposes. However, objective eye movement recording techniques also have a serious disadvantage. One generally does not know the location of the fovea with respect to the retinal image of the target. Thus, as advocated by Mackensen (1957) and Ciuffreda *et al.* (1979a), use of both accurate eye movement recordings and visusopic examination results (along with entoptically derived measures of magnitude of eccentric fixation) are essential for a complete, quantitative description of fixation in amblyopic eyes.

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Contrast sensitivity in amblyopia due to stimulus deprivation

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SUMMARY Contrast sensitivity functions for sinusoidal gratings of varying spatial frequency and stimulus duration were determined for both eyes of 2 patients with amblyopia due to early occlusion and lid closure. The amblyopic eyes showed reduced contrast sensitivity over a wide range of spatial frequencies and stimulus durations, and the temporal integration time of the amblyopic eye was increased by comparison with the non-amblyopic eye at high spatial frequencies. When the gratings were flickered at 10 Hz the sensitivity for both flicker and pattern detection was reduced in the amblyopic eye over the entire spatial frequency range. Abnormal flicker perception by the amblyopic eyes was also evident in the reduced photopic luminosity functions of these patients.

Amblyopia is a condition in which there is a decrease in visual acuity caused by form deprivation and/or abnormal binocular interaction for which no organic cause can be detected by the physical examination of the eye and which in appropriate cases is reversible by therapeutic measures (von Noorden, 1977). Much of what is currently known about the effects of form deprivation, strabismus, and anisometropia on the developing nervous system comes from electrophysiological studies of cats or monkeys reared with experimentally induced amblyopia. These experimental manipulations result in marked disruption in cortical physiology, cell shrinkage in the LGN, and severe amblyopia (Wiesel and Hubel, 1963; von Noorden, 1977). However, it is not clear whether strabismus and form deprivation (due to lid suture or occlusion) affect similar cell populations in the visual pathway. There is evidence that the effects of monocular lid closure are selective for the Y or transient cells (Sherman *et al.*, 1972), while in kittens reared with unilateral strabismus the X or sustained cells appear to be most affected (Ikeda and Wright, 1976).

Amblyopia due to strabismus or anisometropia in man, has been much studied both psychophysically and electrophysiologically. In amblyopias of this type the 'light-sense' of the amblyopic eye is generally considered to be normal. Wald and Burian (1944) investigated dark adaptation and scotopic and photopic luminosity in persons with strabismic amblyopia and showed that these functions are

similar in amblyopic eyes and non-amblyopic eyes, the similarity indicating that the visual receptors function normally in the amblyopic eye. From these data they postulated a dissociation of form vision and light perception. Burian (1969) suggested that amblyopia represents a defect of form vision at photopic levels, which may be explained by a reduction in the lateral inhibition which is necessary for visual acuity but not for simple light perception. Visual evoked response (VER) studies of strabismic and anisometropic amblyopia similarly suggest that the responses to unpatterned stimuli are relatively unaffected in the amblyopic eye, while pattern responses are markedly abnormal (Spekreijse *et al.*, 1972; Sokol and Bloom, 1973; Levi, 1975; Levi and Walters, 1977). On the other hand several investigations (Awaya *et al.*, 1973; Tsutsui *et al.*, 1973; Levi, 1976) have shown that VERs elicited by both patterned and unpatterned stimuli may be abnormal in amblyopia due to form deprivation.

In order to understand better the nature of amblyopia of varying aetiologies it is important to characterise the performance properties of such eyes to a wide range of spatially and temporally modulated stimuli.

It has recently been reported that persons with naturally occurring amblyopia due to strabismus and/or anisometropia show abnormal contrast sensitivity over a wide range of spatial frequencies, with the deficit being most evident at high spatial frequencies (Levi and Harwerth, 1977; Hess and Howell, 1977), and these findings are reflected in the VER at suprathreshold contrast levels (Levi and Harwerth, 1978). When gratings are temporally

modulated, either in counterphase or flickered, both flicker and pattern detection are similarly affected in the amblyopic eye (Hilz *et al.*, 1977; Levi and Harwerth, 1977; Wood and Kulikowski, 1978), however, for low spatial frequency gratings, at high rates of temporal modulation (for example, 10 Hz), both the flicker and pattern thresholds of the amblyopic eye are fairly similar to those of the non-amblyopic eye.

So far there have been no detailed psychophysical investigations of patients with amblyopia due to form deprivation. Here we present the results of studies of spatial and temporal processing in 2 patients with amblyopia due to form deprivation in order to characterise their performance properties and to ascertain whether the visual deficits resulting from form deprivation are similar in nature to those found in strabismic and anisometropic amblyopia.

Patients and methods

The patients were 2 young adults with unilateral amblyopia due to form deprivation. Both had clear media and normal fundi, and were appropriately corrected for refractive error. Detailed histories were available for both.

Patient *A*, male, aged 23, had a congenital ptosis of the left eye. Surgery at the age of 2 years was unsuccessful, and it was not until aged 6 that the condition was surgically corrected. A careful case history, ophthalmological records, and examination of early photographs suggested that during this period the eye was essentially closed. The Snellen acuity of the amblyopic eye was 20/100. Therefore the primary aetiological factor in this patient appeared to be lid closure.

Patient *B*, female, aged 29, was a congenital right esotrope. At age 9 months a programme of constant, total, direct occlusion of the left eye (that is, the non-deviating eye) was instituted. The patient wore a black patch 24 hours a day except for occasional visits to the eye specialist. The patch was changed in the dark. Strabismus surgery to the right eye was performed at age 11 months, and occlusion was continued for a further period of 11 months. Her Snellen acuity at the time of these investigations was 20/200 with the left eye, which was presumably a result of the prolonged occlusion early in life. While the period of susceptibility to the effects of monocular occlusion is not well defined in man, it appears to extend until at least 4 years of age (von Noorden, 1973). In addition the patient's left eye presently shows 12Δ of exotropia. Both patients had unsteady fixation (particularly patient *B*) but were capable of central fixation.

The methods used were similar to those in our study of strabismic and anisometropic amblyopia

(Levi and Harwerth, 1977). Gratings with a sinusoidal light distribution were electronically generated on an oscilloscope (Tektronix 5103N with P4 phosphor) by the method described by Campbell and Green (1965). A gate to the Z axis allowed the gratings to be presented intermittently, while maintaining a constant mean luminance (10 cd/m²). The screen was viewed at a distance of 114 cm and a circular mask provided a 3° field surrounded by a cone which was similar in colour and brightness to the screen.

At each spatial frequency the contrast was adjusted from below threshold in 1-db steps until threshold was reached. For each contrast threshold the series of 8 measurements yielded a standard error of less than 5%. To investigate spatiotemporal effects the gratings were presented either continuously or intermittently for durations of 500, 50, or 8 ms, at a rate of 1 per second, or were flickered at a rate of 10 Hz with an equal duty cycle.

Results

Fig. 1 shows the contrast sensitivity functions for both eyes of both patients for 4 different temporal conditions. The gratings were on continuously for 500, 50, and 8 ms. For both the non-amblyopic and amblyopic eyes it is apparent that contrast sensitivity is a function of stimulus duration and that the low spatial frequency attenuation diminishes with shorter stimulus duration. The contrast sensitivity function of the amblyopic eyes differs from that of the non-amblyopic eye in several respects. (1) Contrast sensitivity is reduced over a wide range of spatial frequencies and temporal durations. Only for the low spatial frequencies when the gratings were viewed continuously was the sensitivity of the amblyopic and non-amblyopic eyes similar, particularly the data of Patient *A*. (2) The peak sensitivity was shifted to the left, that is towards lower spatial frequencies. (3) The cut-off spatial frequency was shifted towards the lower spatial frequencies. The inset curves in Fig. 1 show log of ratio of contrast sensitivity of the 2 eyes as a function of spatial frequency. For all 4 stimulus durations the magnitude of the difference between the contrast sensitivity of the non-amblyopic and amblyopic eyes increases as a function of spatial frequency, although less markedly for Patient *B* than for Patient *A*.

To assess further the effects of stimulus duration we determined the contrast sensitivity for gratings of 0.50 cycles per degree (cpd) and 5.0 cpd at 9 different stimulus durations from 6.2 to 500 ms, as well as during continuous viewing of the gratings. Fig. 2 shows a plot of the contrast sensitivity of Patient *A* as a function of stimulus duration on

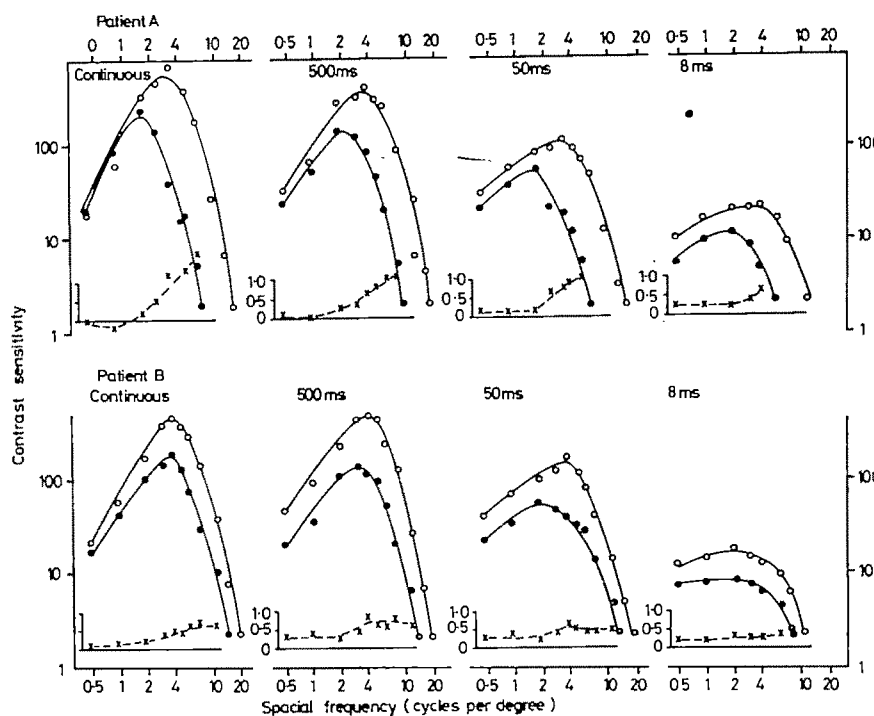


Fig. 1 Contrast sensitivity functions for Patient A (A) and Patient B (B). The open circles are the data for the non-amblyopic eye, closed circles show the data for the amblyopic eye. The duration of the stimulus is, from left to right, continuous, 500, 50, and 8 ms. The inset curves show the log of the ratio of the contrast sensitivity of the amblyopic to the non-amblyopic eye as a function of spatial frequency

log-log co-ordinates. Fig. 2A is for a 0.50 cpd grating, and Fig. 2B for a grating of 5.0 cpd. Each data point is the mean of 10 threshold measurements. For both spatial frequencies the data appear to be divided into 2 segments and straight lines were fitted to the data as previous investigators have done (Breitmeyer and Ganz, 1977). It is apparent that for both eyes contrast sensitivity increases as a function of stimulus duration and that the durations for which the contrast versus duration reciprocity holds is longer for 5.0 cpd than for 0.50 cpd (as indicated by the arrow). Breitmeyer and Ganz (1977) have similarly shown that integration time increases with the spatial frequency of the grating.

The effect of amblyopia on the reciprocity function also varies with spatial frequency. For the 0.50 cpd grating (Fig. 2A), the slopes of the reciprocity function and the integration time of the 2 eyes are similar, with the sensitivity of the amblyopic eye being uniformly reduced by approximately 2/10 log unit with respect to the non-amblyopic eye for most stimulus durations. When the gratings were on continuously, the sensitivity of the non-amblyopic eye was reduced while the sensitivity of the amblyopic eye was not diminished. Apparently, any temporal transient, regardless of duration, enhances the sensitivity of non-amblyopic eyes for low spatial frequency gratings.

Fig. 2B shows the data for a 5.0 cpd grating. For

this higher spatial frequency grating the data of the amblyopic eye differ from those of the non-amblyopic eye in 3 ways: (1) The slope of the accelerating portion of the curve is considerably lower; (2) the integration time of the amblyopic eye is approximately twice as long as that of the non-amblyopic eye; and (3) the contrast sensitivity of the amblyopic eye is greatly reduced by comparison with the non-amblyopic eye. This reduction varied from 7/10 log unit at short exposure durations to over 1 log unit at long exposure durations.

Thus the amblyopic eye shows reduced sensitivity to spatial contrast over a wide range of spatial frequencies and temporal durations, with the abnormality being most marked for high spatial frequencies. In addition, the temporal integration time for high spatial frequencies is greatly increased in the amblyopic eye, being approximately twice as long as that of the non-amblyopic eye.

When low spatial frequency sinusoidal gratings are alternated in counterphase or switched on and off repetitively at threshold, the spatial structure is not evident but rather there is an appearance of flicker or movement. If the contrast is increased further, the individual bars can be detected—the pattern recognition threshold (Van Nes *et al.*, 1967; Keesey, 1972; Kulikowski and Tolhurst, 1973). At higher spatial frequencies (greater than about 4 cpd) gratings which are temporally modulated at threshold

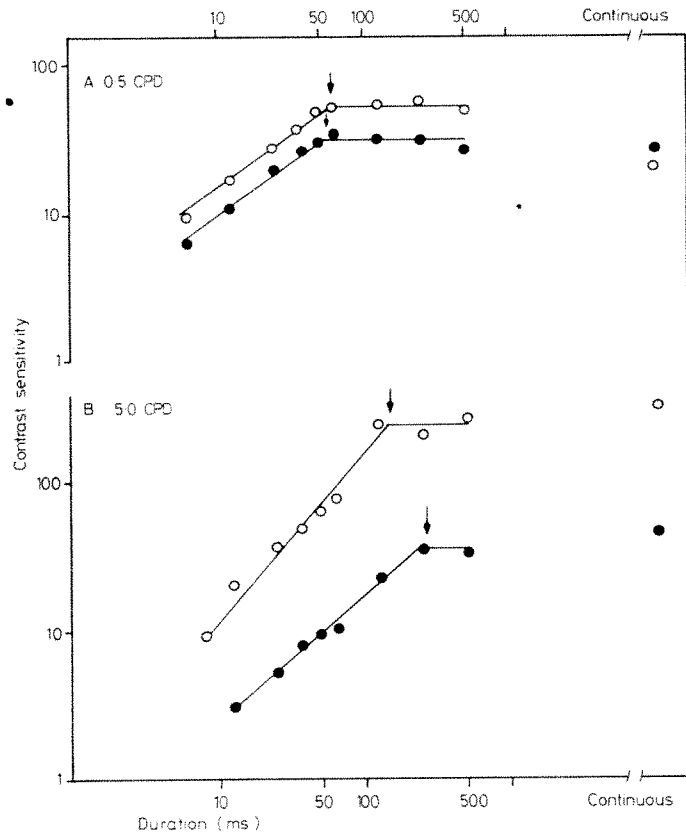


Fig. 2 Stimulus duration versus contrast sensitivity functions for the non-amblyopic (open circles) and amblyopic (closed circles) eyes of Patient A: (A) for a 0.5 cpd grating, (B) for a 5.0 cpd grating

appear indistinguishable from stationary gratings of similar spatial structure (Kulikowski and Tolhurst, 1973).

In order further to evaluate spatiotemporal properties in these patients, we determined contrast sensitivity functions for gratings which were switched on and off at a rate of 10 Hz using the method described by Kulikowski and Tolhurst (1973). The data are shown in Fig. 3. Data for the non-amblyopic eye are shown by the open symbols and for the amblyopic eyes by the solid symbols. The circles show the sensitivity for detecting the stimulus based on the appearance of flicker or movement. The triangles show the sensitivity for pattern recognition.

In Patient A (Fig. 3A) for both the amblyopic and non-amblyopic eyes it is clear that at low spatial frequencies detection (based on flicker or apparent movement) thresholds are lower (that is higher sensitivity) than the thresholds for pattern recognition, and show considerably less low frequency attenuation. Above spatial frequencies of 3 to 4 cpd, the patterns were recognisable at threshold and appeared to be stationary, and the contrast had to be further increased to determine flicker threshold

for high spatial frequency gratings. It is interesting that at all spatial frequencies tested both flicker detection and pattern recognition sensitivities of the amblyopic eye to the 10 Hz flickering stimuli are reduced approximately equally.

Both flicker and pattern detection thresholds were determined over the entire spatial frequency range for Patient B and the data are shown in Fig. 3B. For spatial frequencies below 3 cpd the non-amblyopic eye shows greater sensitivity to flicker than to pattern detection, while at higher spatial frequencies pattern recognition occurs at the detection threshold, and the contrast must be further increased for the flicker to be detected. The data for the amblyopic eye of Patient B are particularly interesting in that at all spatial frequencies above 0.50 cpd she was unable to reach pattern detection threshold. In addition, at all spatial frequencies flicker detection sensitivity was reduced in the amblyopic eye in contrast to that of the non-amblyopic eye.

To investigate further the low spatial frequency flicker responses of these patients we determined photopic luminosity curves, using a flicker criterion (Harwerth and Levi, 1978). The test field was 1° in

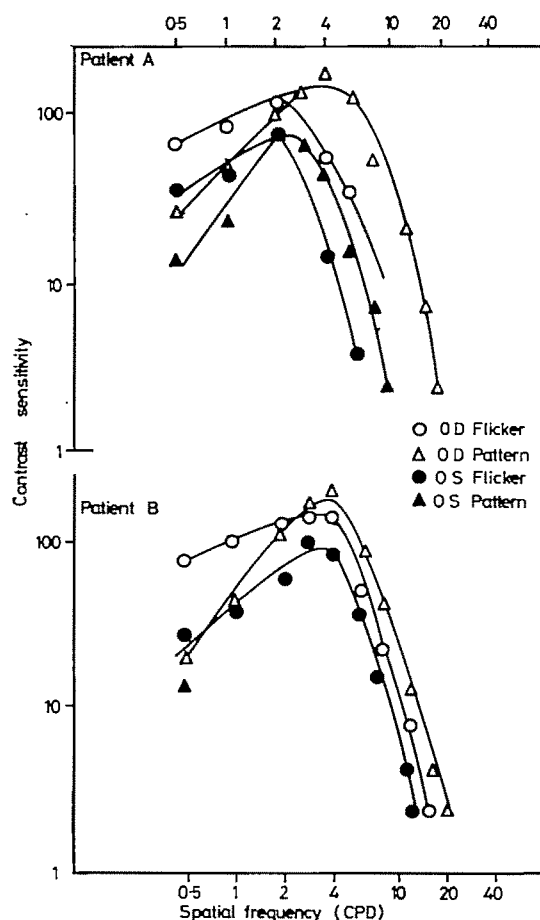


Fig. 3 Contrast sensitivity functions for Patients A and B for gratings flickering at 10 Hz. Flicker and pattern thresholds are shown for the non-amblyopic (open symbols) and amblyopic (closed symbols) eyes

diameter in a dark field with a 25 Hz flicker rate. The patient controlled an optical wedge which was varied to reach critical fusion frequency (CFF) in alternating ascending and descending trials. A total of 10 threshold values were obtained at each wavelength. The data for the 2 patients are shown in Figs. 4B and 4C respectively, while for comparison data from both eyes of an anisotropic amblyope are shown in Fig. 4A. The data for the non-amblyopic eyes are shown by the open circles and the data for the amblyopic eyes by the filled circles. The solid line is the Commission Internationale de l'Eclairage photopic luminosity curve for the standard observer.

It is interesting to note that for the patient with anisotropic amblyopia (OD 20/200, OS 20/20) the data for the 2 eyes are rather similar, while for

both patients with amblyopia due to form deprivation the data of the amblyopic eyes show a reduction in spectral sensitivity across all wavelengths.

Discussion

The results suggest that amblyopia due to form deprivation involves more than a simple reduction in detection of high spatial frequencies, since the reduction in contrast sensitivity of the amblyopic eye

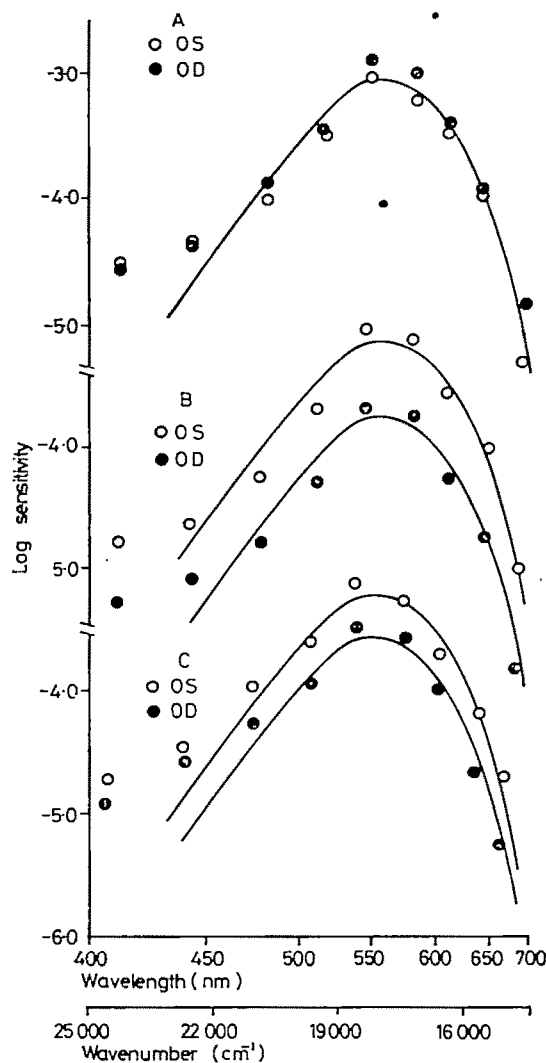


Fig. 4 Photopic luminosity functions for anisotropic amblyope (A), and for Patient A (B) and Patient B (C). The open circles show the data for the non-amblyopic eyes and the filled circles are the data for the amblyopic eyes. The lines are the CIE photopic luminosity curve for the standard observer

is also evident for middle and low spatial frequencies and a wide range of temporal conditions. In addition, the temporal integration time of the amblyopic eye for high spatial frequency gratings is increased. The similarity of these deficits to those found in strabismic and anisometropic amblyopia suggest that there may be common aetiological factors in strabismic and anisometropic amblyopia and form deprivation amblyopia; however, the flicker data also suggest some differences in the performance characteristics of these different categories.

In the 2 patients studied the effects of lid closure and occlusion resulted in severe amblyopia with a loss of sensitivity to spatial contrast over a wide range of spatial frequencies. Their data differed from the strabismic and anisometropic amblyopes in that their contrast sensitivity functions did not show the reduction in low spatial frequency attenuation characteristic in the data of the strabismic and anisometropic amblyopes (Levi and Harwerth, 1977). In addition, the sensitivity to flickering gratings of low spatial frequencies was considerably reduced, whereas the strabismic and anisometropic amblyopes showed essentially identical pattern and flicker detection sensitivity for 0.50 cpd gratings flickered at a rate of 10 Hz; moreover, for Patient B we were unable to measure pattern detection thresholds for spatial frequencies above 0.50 cpd. The anomalous responses to low spatial frequency flickering stimuli were also reflected in their reduced photopic luminosity functions, while strabismic and anisometropic amblyopes showed essentially identical curves for the 2 eyes (Harwerth and Levi, 1978), a finding in agreement with those of Wald and Burian (1944). These data suggest the possibility of a more widespread deficit in amblyopia due to lid closure or occlusion, namely one involving both the pattern and luminance channels.

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Dosage and Administration
Adult: One drop to be instilled into the eye once or twice daily or at the discretion of the physician. Children: At the discretion of the physician.

Contra-Indications, Warnings, etc.

GANDA should not be used in the case of a narrow angle between the iris and cornea as pupillary dilation may precipitate angle closure.

Occasionally a patient may complain of orbital discomfort or red eye (hyperaemia).

Rarely, headache, irritation and local skin reactions may occur. As with other adrenaline preparations, melanosis may occasionally occur, but this has no pathological significance.

Systemic effects are rare but include tachycardia, extrasystoles, and elevation of blood pressure.

One clinical investigator has reported that in two cases out of 21, a paradoxical increase in I.O.P. occurred for which no explanation was offered.

Some degree of ptosis may represent an adverse effect in glaucoma, but will usually respond to a reduction in dosage or in the frequency of administration.

At prolonged high dosage a tendency to superficial punctate keratitis has been reported, responding either to a reduction in dosage or interruption of treatment.

When used in conjunction with miotics, GANDA should follow the miotic after an interval of 5-10 minutes.

Pharmaceutical Precautions

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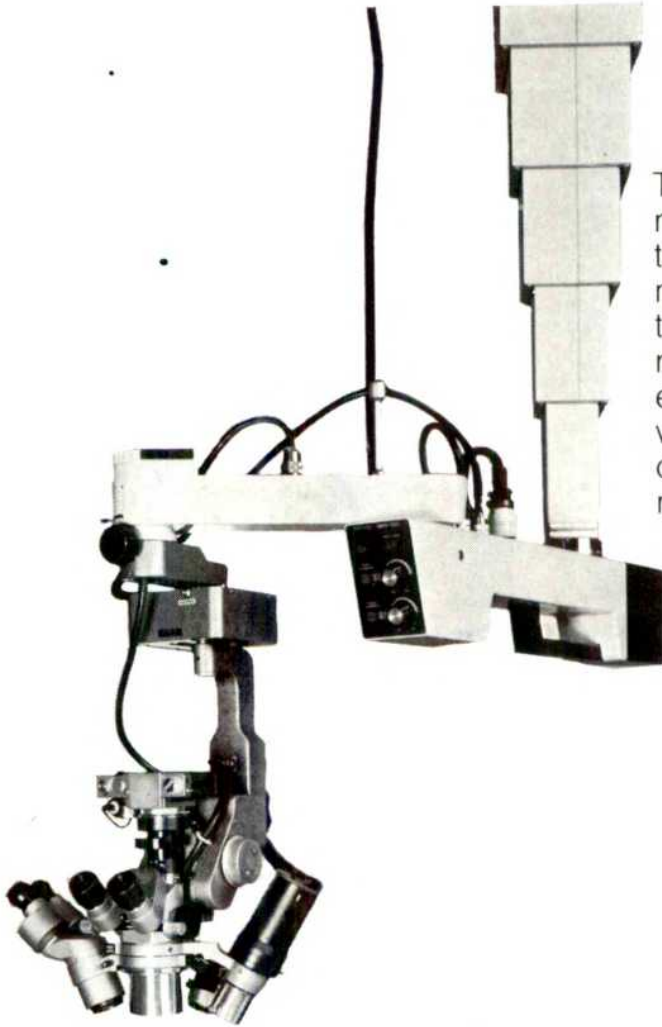
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Effect of age on Arden grating acuity

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SUMMARY Arden grating test scores were obtained for 100 normal subjects under standardised testing conditions. While previously published ranges of interocular congruity were corroborated, a significant increase in test scores with increasing age was noted. This effect of age has not been previously reported. Physiological considerations suggest that such age dependency might have been expected. It is suggested that ranges of normal values be established for each of several age groups.

Arden (1978) has developed a practical clinical test of contrast sensitivity, commercially available as Arden Gratings. This book of 6 test plates displays vertical bar gratings of different frequencies (cycles/degree), increasing in sinusoidal contrast as one moves down each plate. The variations in grating frequencies and contrasts allow testing of several points along the modulation transfer function (the graph of contrast sensitivity at different spatial frequencies). Contrast sensitivity has been shown to be a sensitive indicator of visual disturbance in many ophthalmological and neurological diseases (Bodis-Wollner, 1972; Sjöstrand and Frizen, 1977; Wolkstein *et al.*, 1978), and the Arden Grating test has already demonstrated its clinical usefulness in early glaucoma (Arden and Jacobson, 1978) and minimal demyelinating disease (Arden and Gucukoglu, 1978).

This is a subjective test, and the numerical score achieved may be affected by several factors, such as ambient lighting, the rate of exposure of the grating pattern to the subject, the willingness of the subject to 'take a chance' (guess) or wait until certain before responding, and so on.

Despite the presence of such potential variables early clinical trials in an unsophisticated population (Minassian *et al.*, 1978) show this test to be of great practical value when screening for ocular disease. Arden has reported that 'in the age range 11 to 70 there was no influence of age on the results, grouped in decades of age' (Arden, 1978). To the contrary, we have found that test scores rise (become worse) with increasing age and consider that age-corrected ranges of normal must be established for each set of examination protocols.

Patients and methods

Hospital personnel and visitors free of ocular disease other than corrected refractive error and/or presbyopia were tested by the same examiner in the same room under identical lighting conditions. Visual acuities (with correction where appropriate) at the test distance (the patient's reading distance) were J1 or better. The plates were exposed at the same constant rate for all subjects. Tests were repeated only if anomalous results were obtained and, if not reproducible, were eliminated from tabulation. A total of 100 patients (200 eyes) were examined. Ages by decades were as follows: 8 patients were in their second decade, 38 in their third decade, 24 in their fourth, 14 in their fifth, and 16 were in their sixth decade; 87 patients were female, and 81 were Caucasian.

Results

Arden (1978) has stated that grating test scores greater than 82 indicate an abnormality. While most of our patients with higher scores were over 40 years of age, 6 under 40 had scores in one or both eyes exceeding 82. This may represent a difference in testing conditions. Indeed, our scores in general tended to be slightly higher than the averages obtained by Arden. Arden also states that interocular differences greater than 11 indicate an abnormality, and in this (a comparison of 2 eyes under identical test conditions) we basically agree. Only 7 of our patients showed interocular differences of greater than 11 (only 1 greater than 13, and on further testing this patient was found to have a microtropia in the eye that scored 14 points worse) (Fig. 1). However, we found a definite increase in test scores (decrease in contrast sensitivity) with increasing age

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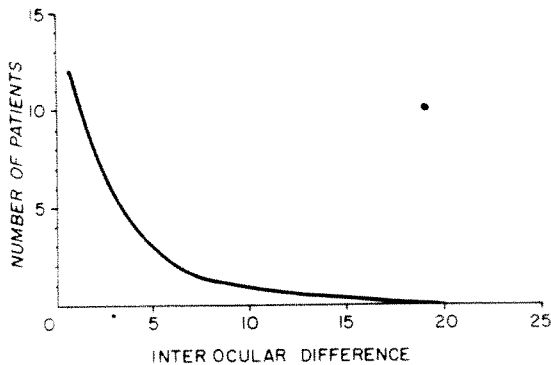


Fig. 1 Averaged curve of interocular difference in scores of subjects studied

(Fig. 2). Average interocular differences did not increase with advancing age. Average scores in the second decade were 69.16, with an average interocular difference (AID) of 4.06, 70.76 (AID 2.93) in the third decade, 73.20 (AID 4.64) in the fourth decade, 79.46 (AID 4.64) in the fifth decade, and 88.23 (AID 4.63) in the sixth decade.

Discussion

Although surprisingly little work has been done on visual changes with increasing age, it is known that visual acuity deteriorates after the age of about 45 years (Weale, 1975). This is not surprising in view of factors such as senile miosis, lenticular and other medial changes, cellular loss in the brain (and retina?) with ageing, etc. Physiological functions such as macular recovery after photostress have been shown to deteriorate with age (Severin *et al.*, 1967; Henkind and Siegel, 1967). It would be surprising if contrast sensitivity remained unaffected. Indeed, results in our patients show contrast sensitivity thresholds to rise with age despite excellent Snellen acuity. Snellen optotypes are high-contrast targets. One would expect abnormalities in distinguishing such blatant targets to occur with more advanced stages of degenerative changes than one would hope to uncover with subtle variations in contrast.

We found advancing age to be associated with increase of scores in all test plates irrespective of spatial frequency, a result implicating the contrast function rather than acuity. Both coarse and fine gratings were seen by our older patients (on average) only when contrast was increased over that necessary for younger patients.

The Arden grating test is an elegantly simple method of evaluating an important and hitherto

usually neglected parameter of visual function. However, as it is a subjective test requiring active participation by the patient, people administering the test should probably establish their own ranges of normal values until lighting and rate of presentation are standardised. Previously published values concerning interocular variability are probably generally valid. Lighting and rate of stimulus presentation should be essentially the same for both eyes, and internal test consistency should yield reproducibility in this regard. Normal values, however, definitely appear to be age dependent, at least in our patients. Advancing age affects nearly all areas of physiological performance, and

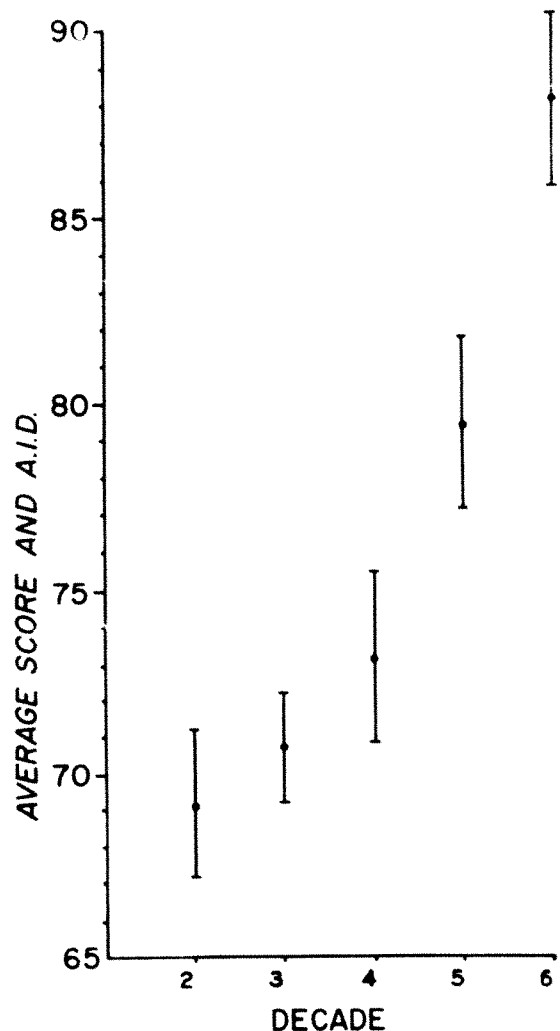


Fig. 2 Average score and average interocular difference (AID) by decade

contrast sensitivity, as measured by the Arden Grating test, is no exception. Consequently, normal values must be developed for each age group.

I thank Judy Bacon, RN, for her skilled administrative and technical help in this study.

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Comparison of Snellen acuity, VER acuity, and Arden grating scores in macular and optic nerve diseases

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SUMMARY Patients with various macular and optic nerve abnormalities underwent Snellen acuity, transient VER acuity, and Arden grating testing. Snellen acuity was the coarsest of the 3 evaluations, generally falling after Arden scores and VER acuity had already undergone significant degradation. The Arden gratings appeared to be the most sensitive of the 3 tests, equalling VER performance in optic nerve diseases and surpassing it in macular diseases. Variations in results between the different tests are generally understandable if one considers the functions tested by each and the anatomical derangements caused by the diseases in question. The Arden grating test appears to be an excellent and sensitive screening test for central visual disturbances.

Visual function has classically been defined by Snellen acuity, supplemented by visual field testing. Indeed, our definitions of legal blindness are couched in terms of Snellen acuity level or visual field subtended. These subjective tests have served, as they are easy to standardise and require a minimum of instrumentation. They may perhaps be taken as measures of the 'quantity' of vision. More difficult to standardise, and until recently much more difficult to evaluate, are estimations of the 'quality' of vision. Parameters such as contrast sensitivity at different spatial frequencies (a modulation transfer function) would provide one perspective on this subject. The recently developed Arden gratings¹ provide a practical clinical method of evaluating such visual sensitivity.

A person's visual perception of the world may be altered in various ways by disease states. Optic nerve and macular diseases lead to visual disturbances that are often (in optic nerve disease) or usually (in macular disease) not relevant to description in visual field terminology. Likewise, macular and optic nerve disturbances may lead to significant functional loss which is not accurately reflected by tests of high-contrast resolution such as Snellen optotypes.

Snellen optotypes, VER responses to alternating checkerboard stimuli, and Arden contrast sensitivity grating charts are not equivalent visual stimuli.

Contrast, visual field subtended, and dynamism of presentation differ among these tests, which are measuring somewhat different visual functions. 'Acuity' according to each of these parameters, while hopefully showing congruence in health, would be surprising in disease. Indeed, we have found wide variations between Snellen acuity, VER acuity, and Arden scores in patients with optic nerve and macular diseases, variations which for the most part are predictable from consideration of the functions being evaluated and the pathology under evaluation.

Materials and methods

Patients with macular or optic nerve diseases were examined wearing their refractive corrections, including near additions where appropriate. Snellen acuity was recorded in the conventional manner, utilising a projected image at a distance of 20 ft (6 m) in a darkened room. Arden grating scores were obtained under standardised lighting conditions (7 ft-candles), all tests being performed by the same examiner to ensure uniformity of test administration.

VER 'acuities' were obtained monocularly with monopolar leads placed 1 cm above the inion, referenced to the ipsilateral mastoid process, and recorded with the Nicolet CA-1000 system with television pattern generator. High-contrast black and white alternating check stimuli were presented at an alternation rate of 3.75 Hz, and 128 transient

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responses covering the 200 ms following each alternation were averaged. At our testing distance the entire screen subtended $10^{\circ} 42'$ horizontally and $8^{\circ} 1' 30''$ vertically. While it is known that the latency of the recorded VER responses increases as the limits of resolution are approached,^{2,3} the major change which occurs is a reduction in amplitude of the recorded VER.⁴ We were interested in the limit of resolution rather than a 'normal versus abnormal' differentiation, and therefore end points were taken to be the smallest checks yielding recognisable responses (check sizes were reduced stepwise by half). Latencies did in fact increase as the patterns became more difficult for the patients to discern.

Some patients did not produce detectable VER responses to our patterned stimuli, and in these patients it was necessary to use light flash (luminance) stimuli in order to elicit a recordable VER. The 3 intensities of luminance used, in increasing order of brightness, were 'on-off' (the entire television screen flashing on and off), and the S_1 and S_{16} settings on the Grass PS₂₂ photostimulator with the stimulating light placed 4 ft (1.2 m) from the subject. These light flash (luminance) VERs, while obviously not measuring precisely the same function as the constant-luminance pattern reversal VERs, were recorded and averaged in an identical manner; 128 transient responses obtained from a monopolar electrode placed 1 cm above theinion were averaged for each monocular recording.

Our patient sample included a variety of macular and optic nerve diseases. Among these were senile macular degeneration, macular dystrophies, cystoid macular oedema, premacular fibrosis, retrobulbar neuritis, ischaemic optic neuropathy, traumatic neuropathies, tumours, etc. Patients with significant medial opacities, for example, cataracts, corneal scars, etc., were excluded. Patients ranged in age from 8 to 86 years, 75% being between 40 and 80 years old.

Results

In general, Snellen acuity proved most resistant to degradation by less severe macular and optic nerve disease states. This familiar test, using test symbols intimately known to patients and presented for recognition in high contrast at the patient's own chosen rate of response, did not prove to be a good screening test for macular or optic nerve diseases.

VER responses to alternating high-contrast black and white checks, obviating need for conscious recognition, interpretation, or ability to use clues (for example, 'could be E, B, O, or D, but certainly isn't L or P or T') were intermediate in sensitivity.

While Snellen acuity was sometimes more sensitive than VER acuity in macular diseases, 44% of examined patients showing relatively greater decrease in Snellen acuity (Fig. 1), the VER was definitely a more sensitive test in optic nerve diseases, where 82% showed greater abnormality on VER testing (Fig. 2). The superiority of the VER in comparison to Snellen testing in optic nerve disease has been shown by many investigators⁵⁻⁷ using delayed VER responses as the criterion of abnormality. The current study provides evidence that the same is true using loss of recordable VER responses to

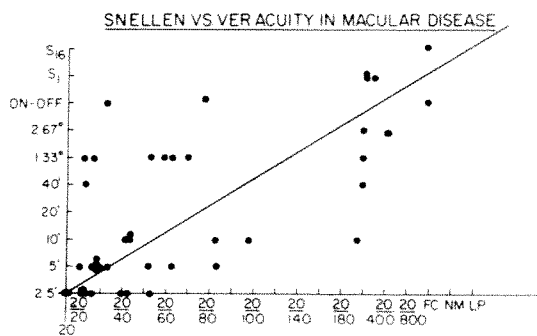


Fig. 1 Snellen acuity (abscissa) compared with VER acuity in patients with various macular diseases. On-off, S_1 , and S_{16} on ordinate scale (Figs. 1, 2, 5, and 6) refer to luminance VER stimuli (recorded for patients in whom no detectable response was obtained to large check pattern-reversal stimuli). In this and following figures the diagonal line runs from good acuity or score (lower left) to very poor acuity or score (upper right). 56% of data points lie above the diagonal, representing relatively greater degradation of VER acuity, while 44% (below the diagonal) show relatively greater fall-off in Snellen acuity.

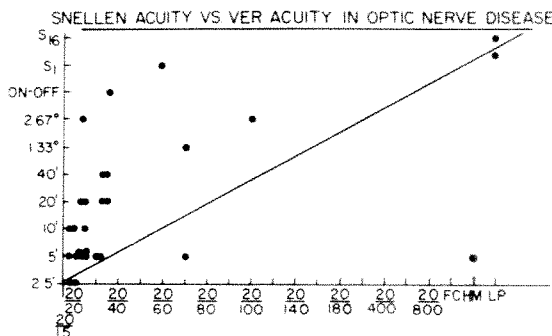


Fig. 2 Snellen acuity (abscissa) compared with VER acuity in patients with optic nerve diseases. 82% of data points lie above diagonal, showing relatively greater sensitivity of VER acuity to diseases of the optic nerves.

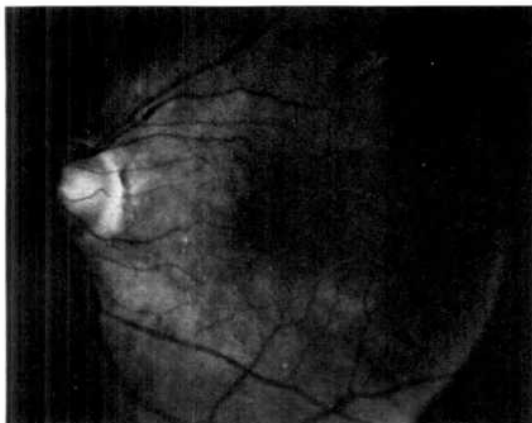


Fig. 7 Fundus photo OS of patient with surface wrinkling retinopathy.

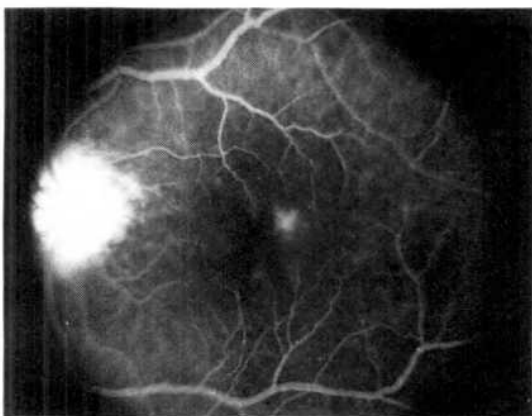


Fig. 8 Late-phase (10 minute) fluorescein angiogram of patient 6 weeks postcataract extraction with resolving cystoid macular oedema. Slight residual leakage can be seen.

OD secondary to a pituitary adenoma was noted to have 20/30—Snellen acuity OD, 20/20 OS. Arden grating scores were 63.5 OD, 62.5 OS—both normal. VER responses showed poor voltage OU, with responses detectable to 20' checks OS, but not OD. Another patient, a 39-year-old male with resolving retrobulbar neuritis OS, had Snellen acuities of 20/20 OD, 20/40+ OS; with Arden scores of 66 OD, 125 OS (being completely unable to distinguish the gratings on plates 5–7 OS). VER testing was normal with 2.5' checks OD, but showed no detectable response OS to 80' checks, and a delayed response to the stimulator screen light going on and off.

While Snellen acuity measurements seemed as useful as VER acuity measurements in macular

diseases (Fig. 1), both paled in comparison with Arden test results in early detection of macular (image detection) dysfunction. For example, a 71-year-old female had surface wrinkling retinopathy OU (Fig. 7). Snellen acuity was 20/30 –2 OD, 20/60 OS. VER responses could be obtained to 5' checks with either eye. However, the lower contrast of the Arden gratings was completely nondiscernible with either eye (score of 150 OU).

'Denser' anatomical lesions such as the macular degenerations tended to affect VER acuity as well as Arden scores. For example, a 54-year-old male was 6 weeks after cataract extraction OS, with resolving cystoid macular oedema demonstrated by fluorescein angiography (Fig. 8). Snellen acuity had improved to 20/25 +3. VER responses were small with 40' checks, and were nonrecordable with 20' checks. The Arden score was 123 (plates 6 and 7 were completely missed).

Focal foveal photoreceptor abnormalities would be expected to cause more interference with VER and Snellen acuities (both tests of resolution of macular targets) than with sinusoidally distributed

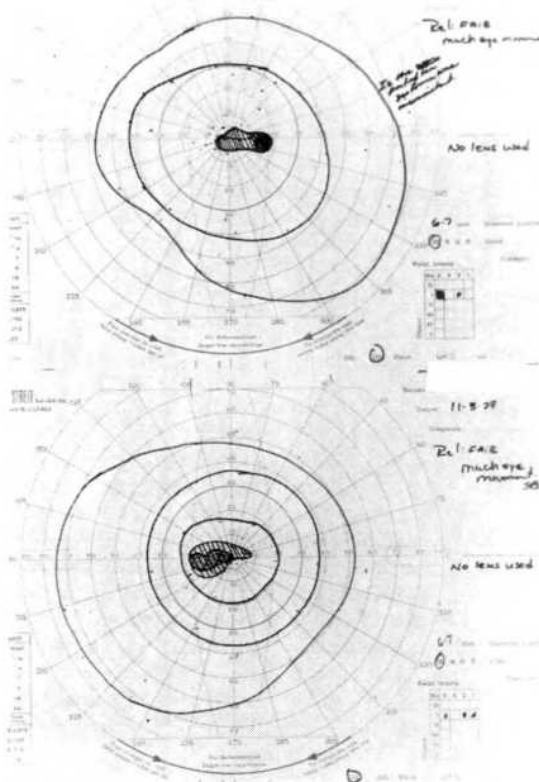


Fig. 9 Visual fields of patient with central form of cone dystrophy, showing discrete central scotomas.

grating contrast changes over the posterior pole, and again, clinical experience tended to confirm this. For example, an 8-year-old with the central form of cone dystrophy made 483 errors on the Farnsworth 100-hue test and had variably recorded Snellen acuities of 20/80—20/200 OD and 20/70—20/100 OS. On VER testing poor responses were obtained to 80' checks with either eye. The central scotomas present (Fig. 9) raised his Arden scores only slightly, to 82.5 OD, 77.5 OS.

Disease cephalad to the occipital cortex should have less effect on VER results recorded at the occipital pole than on subjective responses requiring conscious interpretation and reporting (as would also be true in cases of hysteria or malingering). For example, a 13-year-old female with neurological sequelae of bacterial meningitis in childhood had slight nystagmus, right esotropia, and temporal disc pallor with a mildly amaurotic pupil OD. Snellen acuity was hand movements at 4 ft (1.2 m) OD, 20/70 OS. Arden gratings were not detectable OD (score 150) and scored at 92 OS. However, good VER responses to 5' checks could be recorded using either eye.

VER stimuli may be varied almost infinitely with the aid of electronics. However, stimulating and recording with such apparatus is costly, elaborate, and relatively time-consuming, and is difficult to standardise between laboratories. Furthermore, in following diminishing responses to an end point, VER recordings are ambiguous regarding the presence or absence of small responses superimposed on the background 'noise', and extrapolations are often necessary. VER testing is simply too demanding of time, resources, and interpretation to be practical in the evaluation of large numbers of patients.

The determination of Snellen acuity possesses virtues beyond its ease of performance and universal familiarity. This test requires the subject to provide a correct answer, as opposed to the categorical Arden end point ('yes, I see it'). In following a disease process over time the patient anxious to please his doctor and do well can claim ability to discern the gratings before he actually can, while the Snellen letters require correct elucidation.

By varying stimulus size and contrast the Arden test has incorporated 2 of the major parameters one would be interested in evaluating with sophisticated VER stimulators. The Arden grating test should be easy to standardise, as the only variables are lighting and rate of exposure (presentation) of the test plates. One factor not noted by Arden is the age dependence of 'normal' scores⁸ (Fig. 10), and this must be taken into account (as was done in the present study) when evaluating a subject's

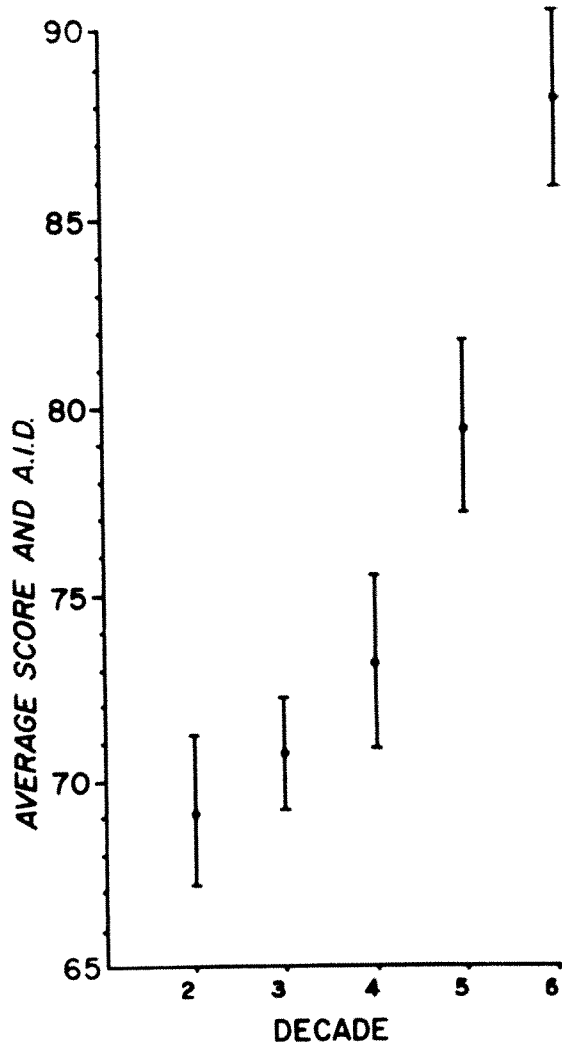


Fig. 10 Average Arden grating scores and average interocular differences (AID) of 100 normal patients grouped by age in decades.

test performance. A simply performed and interpreted clinical test, the Arden gratings appear to offer a sensitive screening test for a host of subtle abnormalities.

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Keratitis due to *Aspergillus flavus* successfully treated with thiabendazole

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SUMMARY A case of *Aspergillus flavus* keratitis treated successfully with 4% suspension of thiabendazole is reported. This seems to be the first case of successful treatment of keratomycosis with thiabendazole. All other reported cases treated with this drug either had their eyes removed or did not retain any useful vision. Its ability to penetrate ocular tissues, ability to remain in concentrations higher than the minimal inhibitory concentration of many fungi, and broad spectrum of activity make it a worthwhile drug for further investigation in keratomycosis.

Various species of the genus *Aspergillus* are among the commonest cause of keratomycosis (Locatcher-Khorajo and Seegal, 1972). There are few reports of keratomycosis treated with thiabendazole and none of its use in aspergillus infections of the eye. We describe the clinical and mycological features of an *Aspergillus flavus* keratitis treated successfully with thiabendazole ocular suspension.

Case report

A 24-year-old man, a country dweller, woke up on the morning of 21 August 1977 with a red and painful right eye. The symptoms gradually worsened, with watering and blurring of vision. He consulted an eye surgeon on 26 August 1977. He was diagnosed as having a corneal ulcer of possibly bacterial origin and treated with atropine and framycetin eye drops 3 times a day. He also received a combination of 400 000 units of penicillin and 0.5 g streptomycin intramuscularly daily. As there was no improvement after 5 days of treatment the patient was referred to one of us (M. P. U.).

Examination on 2 September 1977 showed his vision was only of hand movements, the right upper lid was swollen with blepharospasm, and there was marked circumcorneal congestion. Slit-lamp examination of the cornea showed a dead white plaque of cheesy excrement material (Fig. 1), which came off easily leaving a large fluorescein-staining corneal ulcer. The anterior chamber showed fair number of

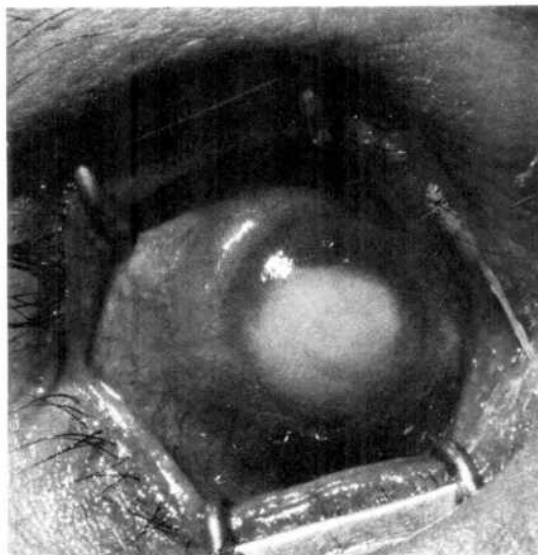


Fig. 1 Patient's eye, showing white plaque

cells, with flare. Intraocular pressures were normal to finger palpation.

The patient was treated with framycetin drops hourly during the day and 2-hourly by night, 2 tablets twice daily of Septrin (sulphamethoxazole, trimethoprim, and co-trimoxazole), and vitamin B-complex and vitamin C twice daily. Once bacterial cultures were reported negative, Septrin was stopped and framycetin reduced to 4 times a day. Fungal culture was reported as a rapidly growing fungus with following sensitivity: amphotericin-

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Fig. 2 *Aspergillus flavus* isolated from patient

B, 15 µg/ml; thiabendazole 5 µg/ml; clotrimazole 1 µg/ml; pimarin 15 µg/ml; miconazole 10 µg/ml; and econazole 5 µg/ml. On 10 September 1977 the patient was started on 4% thiabendazole suspension every 2 hours. Three days later the lesion appeared smaller but a white plaque again formed on the surface of the ulcer. A second corneal scraping on 14 September 1977 showed a fungus on direct smear which was subsequently grown and identified as the one in the original scraping. Thiabendazole was continued. A third scraping taken on 23 September failed to show fungus on direct smear as well as culture.

The patient was allowed home on 28 September with advice to continue thiabendazole 4 times a day with a quiet eye and a vision of 6/18. A week later the eye remained quiet, vision having improved to 6/12 with pinhole. A month later the condition was essentially unchanged. Five months later, on 17 March 1978, he still had a quiet eye with a vision of 6/12 with pinhole, having been on no medication for 3 months. A faint corneal nebula remains.

MYCOLOGICAL STUDIES

A smear of the corneal scraping was examined microscopically by direct wet mount and Gram's stain. Under magnification of 100× both slides showed abundant presence of branching, thick-walled fungi. Another portion was inoculated into a Sabouraud's dextrose agar (SDA) slant at the time of scraping. Incubation at room temperature showed growth of a flat, velvety, white fungal colony. With further incubation the colony developed a yellow-green colour, with radial furrows. The reverse was

golden in colour. Microscopically (Fig. 2) it showed growth of septate hyphae with unbranched conidiophores terminating in an enlarged conidial head covered with flask-shaped sterigmata producing chains of conidia. The hyphae were thick-walled and hyaline and the conidiophores rough and pitted. The isolate was consequently identified as *Aspergillus flavus* and this identification was confirmed by Dr Y. M. Clayton at the Institute of Dermatology in London. Sensitivity tests were run on the fungal isolate by the agar slant method (Holt, 1975). A 10 mm colony was suspended in 0.01 M phosphate buffer. This suspension was then used to inoculate tubes of SDA containing 0.5 to 15 µg/ml of the various test drugs with each tube receiving a loopful of the suspension. A control tube containing no drug was similarly inoculated. Results were read at 48 hours after incubation at room temperature.

Discussion

Keratomycosis due to the genus *Aspergillus* accounts for nearly 50% of all reported cases of oculomycosis (Locatcher-Khorajo and Seegal, 1972; Jones, 1975). The steady increase in the number of fungal infections has not, however, been matched by an increasing availability of useful antifungals. At the time of writing only 3 antifungal drugs are freely available commercially for use in ophthalmology, namely, amphotericin-B, nystatin, and more recently pimarin. The last, however, has not reached many parts of the world where fungal eye infections are commonly seen. Amphotericin has been shown to have severe corneal and systemic toxicity (Jones, 1975; Upadhyay, in press). Nystatin, because of its inability to penetrate the cornea and lack of absorption from the gut (Goodman and Gilman, 1970) is not of much value in ophthalmology except for the most superficial corneal infections. In countries in which clotrimazole is available this imidazole would appear to be the drug of first choice for aspergillus infections of the eye (Jones *et al.*, 1974). Similarly miconazole and econazole have a high level of activity and are effective against ocular aspergillus (Jones, 1975).

However, we were keen to test a drug which is more freely available in many parts of the world and which is known to be non-irritant to the eye and to penetrate the ocular tissues well from topical administration.

Thiabendazole is a well-known broad spectrum anthelmintic and its in-vitro antimycotic activities were reported by Robinson *et al.* (1964). In-vivo antifungal effects were reported by Fleischmajer *et al.* (1965). Thiabendazole has been shown to be an effective antifungal against both pathogenic and

saprophytic fungi. The latter is of greater relevance to ophthalmologists, as most reported cases of oculomycosis have been caused by saprophytes. Thiabendazole has both fungistatic and fungicidal properties (Robinson *et al.*, 1964). The fungi that are particularly sensitive to the drug are dermatophytes *Microsporium* and *Trichophyton*. Fungi with moderate sensitivity include *Cladosporium*, *Phialospora*, *Fonsecaea*, *Madurella*, and *Parenechacha* (Robinson *et al.*, 1969). Strains of *Aspergillus flavus*, including those known to produce aflatoxins, are highly susceptible. Robinson and his associates reported on thiabendazole's ability to penetrate ocular tissues (Robinson *et al.*, 1966). It has been shown that, if applied locally to the rabbit eye in concentrations up to 4%, it is non-irritating (Robinson *et al.*, 1965). This was confirmed in our case both subjectively by patient inquiry and objectively by daily slit-lamp examination of the eye.

Wilson and his associates investigated the effect of a topical application of thiabendazole in a corneal infection due to *Phialophora verrucosa*. Although in vitro tests had shown the isolate to be sensitive to thiabendazole, this drug could not eradicate the corneal infection (Wilson *et al.*, 1966). Sensitivity of *Fusarium* species to thiabendazole was reported by Jones (1975), but in this case, although infection was eliminated, the eye could not be saved, having to be removed due to advanced fungal malignant glaucoma. Ocular penetration from topical administration has been demonstrated (Robinson *et al.*, 1966). Thirty minutes to 1 hour after application of 20 mg of the ^{14}C drug as 0.5 ml of a 4% suspension the cornea contained 42 to 52 $\mu\text{g/g}$, the aqueous 18 to 28 $\mu\text{g/g}$, vitreous 0.5 to 1 $\mu\text{g/g}$, and the lens 2 to 3.4 $\mu\text{g/g}$.

For the last year we have been testing the in-vitro sensitivity to thiabendazole of various ocular isolates. Of the 27 isolates tested only 6 required thiabendazole in concentrations more than 15 $\mu\text{g/ml}$ (minimum inhibitory concentration 15 $\mu\text{g/ml}$). The other isolates have all been sensitive at concentrations lower than 5 $\mu\text{g/ml}$ (unpublished data). Encouraged by these studies and the reasonable sensitivity (MIC 5 $\mu\text{g/ml}$) of this patient's isolate

to thiabendazole we wanted to see the in-vivo effect of this drug. The result has certainly been encouraging.

Dr L. N. Prasad referred the case. Dr C. M. Anklesaria of Merk, Sharpe & Dohme (India) supplied the powder. The ocular suspension was prepared by Anand Deo Shrestha of the Royal Drugs Ltd. We thank them all. Thanks are also due to Dr Y. M. Clayton of the Institute of Dermatology, University of London, for her help in identification. We also record our gratitude to Dr Y. M. S. Pradhan, medical superintendent of Bir Hospital, for allowing us to report this case and for his constant encouragement.

Our thanks are also due to Professor Barrie R. Jones for his helpful suggestions in the preparation of this paper.

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Trifluorothymidine versus adenine arabinoside in the treatment of herpes simplex keratitis

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SUMMARY Trifluorothymidine (TFT) and adenine arabinoside (ara-A) are effective antiviral drugs with a very low toxicity for the cornea. In our study no difference between these 2 drugs in antiviral activity was noted. The average healing time for TFT was 11.14 days and for ara-A 10.54 days. These data differ markedly from those of other studies. This was the result of the use of additional criteria for healing of the lesion. Not only absence of fluorescein staining of the cornea but also the absence of oedema and cystic changes in the epithelium over the previous ulcer were considered criteria for healing. In addition to clearly defined healing criteria and the healing time we found the interval between the first symptoms and the commencement of the therapy of greatest importance in the clinical evaluation of antiviral drug efficacy. An effort was made to approximate this relationship for TFT and ara-A mathematically.

The introduction of idoxuridine (IDU) in 1962 (Kaufman *et al.*, 1962) was the first rational approach to the treatment of dendritic keratitis. Laibson and Leopold (1964), however, found the effectiveness of IDU to be no greater than that of curettage of the corneal epithelium. Moreover, Jones (1967) found IDU to be toxic when used over a long period, and this is a common experience.

In 1972 Wellings *et al.* (1972) published their results with a new antiviral drug, trifluorothymidine (TFT), and found it to be more effective than IDU. In that trial no toxic side effects were noted. In the same year Pavan-Langston and Dohlman (1972) reported that they found another antiviral drug, adenine arabinoside (ara-A), also to be more effective than IDU.

Coster *et al.* (1976) studied the healing time and the rate of healing of superficial herpetic keratitis treated with trifluorothymidine and adenine arabinoside. These workers were unable to find any difference in the healing time of TFT and ara-A with regard to dendritic keratitis. For amoeboid ulcers, however, they found TFT to be possibly more effective than ara-A.

We have reinvestigated the efficacy of trifluorothymidine and that of adenine arabinoside in 56 cases of dendritic keratitis, paying special attention

to the influence of the length of the interval between the appearance of the first symptoms of the disease and the beginning of treatment and to the age of the patient on the healing time. The investigation was done in a double-blind comparative trial.

Materials and methods

Of a total of 66 patients (43 males and 23 females) with dendritic keratitis, 36 males and 20 females were studied. Three male patients were excluded from the study because of omissions in complying with the examination protocol. An additional 7 patients were excluded from the study because their ulcers failed to heal within 23 days, which was our arbitrary limit. Patients who received steroid medication were excluded from the trial.

Of the patients included 17 males and 11 females were treated with trifluorothymidine and 19 males and 9 females with adenine arabinoside. Treatment was given on an outpatient basis. Each patient received a coded treatment sequentially allocated by the central dispensing unit. The preparations consisted of either 2% trifluorothymidine ointment or 3% adenine arabinoside ointment, both specially prepared for this trial. The ointment tubes were identical in design.

The coded antiviral ointment was given according to the following specifications: Every 4 hours 4 to 5 mm of ointment was to be placed in the lower cul de sac, the first application to be given early in the

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morning, the last at bedtime. In addition scopolamine eyedrops 0.2% were given, usually once or twice daily.

When the epithelial defect of the dendritic keratitis had healed, the treatment was continued for one more week. Healing was defined as the situation in which no staining with fluorescein was observed and no epithelial oedema and cystic changes were present in the epithelium covering the site of the original ulcer. Treatment was discontinued after 22 days. Cases that were not healed after 22 days were not included in the analysis and were considered to be failures. Data were recorded on a history and examination sheet. Follow-up examinations were done with special reference to the condition of the anterior segment of the eye. Fluorescein and Bengal rose staining were done to judge the condition of the epithelium.

Results

Seven out of 63 treated ulcers failed to heal within 23 days, which was our arbitrary limit. These cases were excluded from the analysis. Four of these patients were treated with ara-A and three with TFT. In all these patients the ulcer was initially closed as judged by fluorescein examination, but the epithelium in these cases showed areas of oedema and cystic changes in the area of the healed ulcer. The average number of days it took these cases to heal was 32 days, with a minimum of 23 and a maximum of 54 days. These therapeutic failures represented cases of metaherpes complicating the dendritic ulcers. After clinical recurrence of infection, stromal lesions developed eventually.

Table 1 *Healing time for dendritic ulcers arranged according to treatment, sex, and eye*

TFT				ara-A			
Male		Female		Male		Female	
OD	OS	OD	OS	OD	OS	OD	OS
3	21	21	4	7	21	7	20
8	12	7	13	7	7	2	9
12	16	5	18	12	9	6	13
8	4	6	12	22	7	4	14
13	9		20	14	8		5
16	14		16	16	9		
8	5		6	12	14		
10					14		
13					11		
12					14		
					5		
					6		
Mean	10.3	11.6	9.75	12.71	12.86	10.42	4.75
							12.2

Table 2 *Analysis of main effects: therapy, sex, and eye and their interactions. Analysis of variance*

Nature of effect	Source	Sum of squares	DF	Mean sum of squares
Main factors	Therapy (Th)	5.1607	1	5.1607
	Sex (S)	6.0036	1	6.0036
	Eye (E)	28.8517	1	28.8517
Interactions between pairs of factors	Th $\times$ S	34.3790	1	34.3790
	Th $\times$ E	6.2623	1	6.2623
	S $\times$ E	105.7896	1	105.7896
Interactions between triplets of factors	Th $\times$ S $\times$ E	37.7900	1	37.7900
Residual		1267.3167	48	26.4024
Total		1491.5536	55	

DF = degrees of freedom.

$F_{48}^1 = 4.04$; $\alpha = 0.05$. Note the F value of sex $\times$ eye interaction = $F_{48}^1 = 4.0068$, which is almost significant.

In Table 1 the number of days the dendritic ulcers took to heal are given. The data are classified according to type of treatment, sex, and eye. The average number of days for the dendritic ulcer to heal in the TFT-treated group was 11.14 days and in the ara-A-treated group 10.54 days. The average healing time for males was 11.08 and for females 10.40 days. For the right eyes the ulcers took 10.04 and for the left eyes 11.48 days to heal. None of these differences were statistically significant.

In Table 2 an analysis of variance is given. None of the tested factors or interactions are statistically significant. The sex $\times$ eye interaction is noteworthy; the F ratio with 1 and 48 degrees of freedom at the 5% level is 4.04. The F ratio of the sex $\times$ eye interaction is 4.01 and therefore almost significant at that level. This would imply that herpetic ulcers in the right eye of women would heal more rapidly; this does not make sense. Reviewing the histories of the patients in this category we found that these women received treatment at a very early stage of the disease.

In Fig. 1 the scatter diagram of the relationship between the number of days that elapsed between the appearance of the first symptoms of the disease and the moment treatment was initiated and the number of days it took the ulcer to heal is given for the TFT and ara-A treated groups combined. Correlation analysis shows a highly significant relationship between these 2 quantities. If the TFT group is analysed separately, there is no significant correlation. This was the result of some extremely long healing periods in patients who were treated early. They were 2 patients who developed interstitial infiltrations. Furthermore, these patients received treatment on the fifth day and had ex-

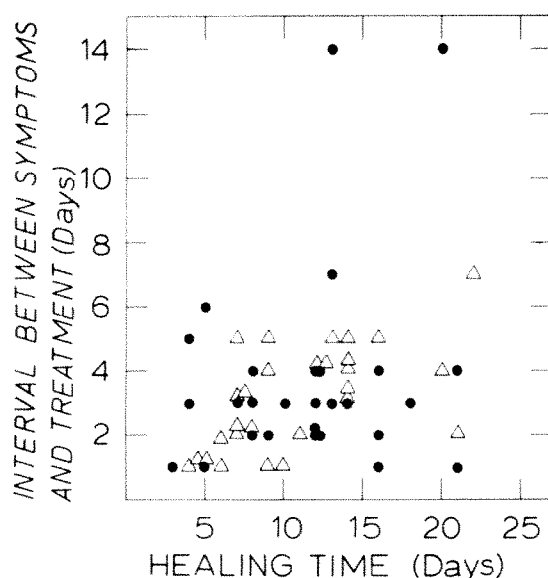


Fig. 1 The relationship between the interval between appearance of first symptoms and initiation of the treatment and the healing time: TFT (●) and ara-A (△)

tremely short healing times. They had a very mild stellate type of herpes keratitis. The healing times of these patients are marked with an asterisk in Table 3.

In Fig. 2 the type of association is shown graphically. It represents the mathematical approximation of the type of association between the interval before treatment and the average healing time of both groups combined. A second-degree curve defined by the formula $y = +11.88 + (2.298 \times$

$-0.485 x^2)$, with origin at day 3 and x-unit equals 1 day, appears to be a good fit.

With regard to the interval before treatment and healing time, the TFT and ara-A group did not differ significantly (Table 4). In Table 5 the importance of very early treatment is shown.

No significant correlation was found between the age of the patients and healing time. Also no statistically significant difference existed in the TFT and ara-A treated groups with regard to age. The average age in the TFT-treated group was 45.18 (33.13–57.23, 99% confidence limits) and for the ara-A-treated group this was 46.14 (33.25–59.02, 99% confidence limits).

In 5 out of 17 patients that received the virostatic treatment longer than 14 days a very mild diffuse epithelial staining was observed with Bengal rose.

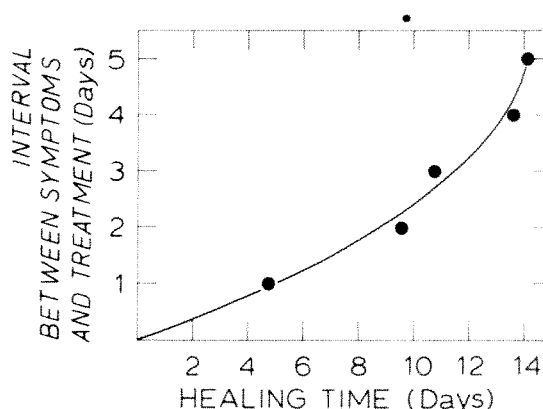


Fig. 2 A second degree curve is a good approximation to the type of relationship between the interval before treatment and healing time

Table 3 The relationship of the interval in days between beginning of symptoms and the treatment, and the healing time of the dendritic ulcer. The figures marked with an asterisk differ very noticeably from the general averages

Healing time in days	Interval between beginning of symptoms and treatment in days									
	1		2		3		4		5	
	TFT	ara-A	TFT	ara-A	TFT	ara-A	TFT	ara-A	TFT	ara-A
	21*	9	16	21	7	7	21	20	4*	7
	3	2	12	7	8	7	12	12	13	9
	16*	5	9	7	18	14	8	9	5*	22
	5	5	8	8	4	14	12	14	20	13
		4	6	11	13		16	14	13	14
			6	6	14			12		16
				6	10					
					12					
Mean	11.25	5.00	9.5	9.4	10.75	10.5	13.8	13.5	11.0	13.5
Number	4	5	6	7	8	4	5	6	5	6
SD	8.6	2.5	3.9	5.4	4.4	4.04	4.9	3.7	6.6	5.3

Table 4 *Analysis of variance of the interval between the beginning of the symptoms and of treatment in the TFT and ara-A treated groups*

Source of variation	Sum of squares	DF	Mean sum of squares
Between treatments	7.1420	1	7.1429
Within treatments	352.5714	54	6.5291
Total	359.7134	55	

$F_{1,54}^1 = 1.09$; not significant.

Table 5 *Differences in healing time and percentage gain if treatment were started 24 hours earlier than stated day*

Day	Average healing time in days	Percentage gain
5	14.14	
4	13.30	5.9
3	11.49	13.6
2	8.71	24.2
1	4.95	43.2

Four of these patients received ara-A and 1 received treatment with TFT. This indicates that both drugs are relatively safe if judged by corneal toxicity.

Discussion

Trifluorothymidine and adenine arabinoside are both very effective antiviral agents. Compared to idoxuridine they are virtually free of toxic reaction. The most striking factor in our study is that the average healing time is considerably longer than that of other similar studies. Coster *et al.* (1976) found the average healing time in his ara-A-treated group to be 5.13 days and for the TFT-treated group 5.75. In our study the healing time for the ara-A-treated group was 10.54 days and that for the TFT-treated group the healing time was 11.14 days.

One of the reasons of this striking difference in healing time could be the criteria for healing. The criterion in the study of Coster *et al.* (1976) was the absence of fluorescein staining of the epithelium. In our study we also included the absence of cystic or oedematous changes in the area of the previous dendritic lesion as healing criteria. These changes are often indicative of persistent viral activity. Our healing criteria necessitated also a longer treatment, which in turn was probably responsible for the absence of true recurrent dendritic ulceration.

The 7 patients that failed to heal within the 22 days' limit all had oedematous and cystic changes in the area of the previous dendrite, but these irregular areas did not stain uniformly with fluorescein. Over the lesion sporadic epithelial erosions were seen, however. After a certain period the epithelium broke down again, and an ovoid superficial lesion with sodden oedematous borders was seen. In addition to these lesions there was a profoundly hypaesthetic cornea. Therefore, they were diagnosed as metaherpetic lesions.

It is true that some 20% of herpetic lesions heal spontaneously within a reasonably short period and without leaving marked corneal scarring. These cases were probably also present in our patient material. As a result of this study we found the interval between the appearance of the first symptoms and the moment treatment was started one of the most important parameters in the study of antiviral drugs. This is very clearly demonstrated by the flat trajectory in Fig. 2. After 4 days the relative efficacy of both TFT and ara-A is markedly diminished as indicated by the steep trajectory. This parameter is neglected in other antiviral drug studies.

We are very grateful for the preparation, coding, and donation of TFT and ara-A by the Laboratories Dr Gerhard Mann GmbH and Dr Thilo & Co. GmbH, respectively.

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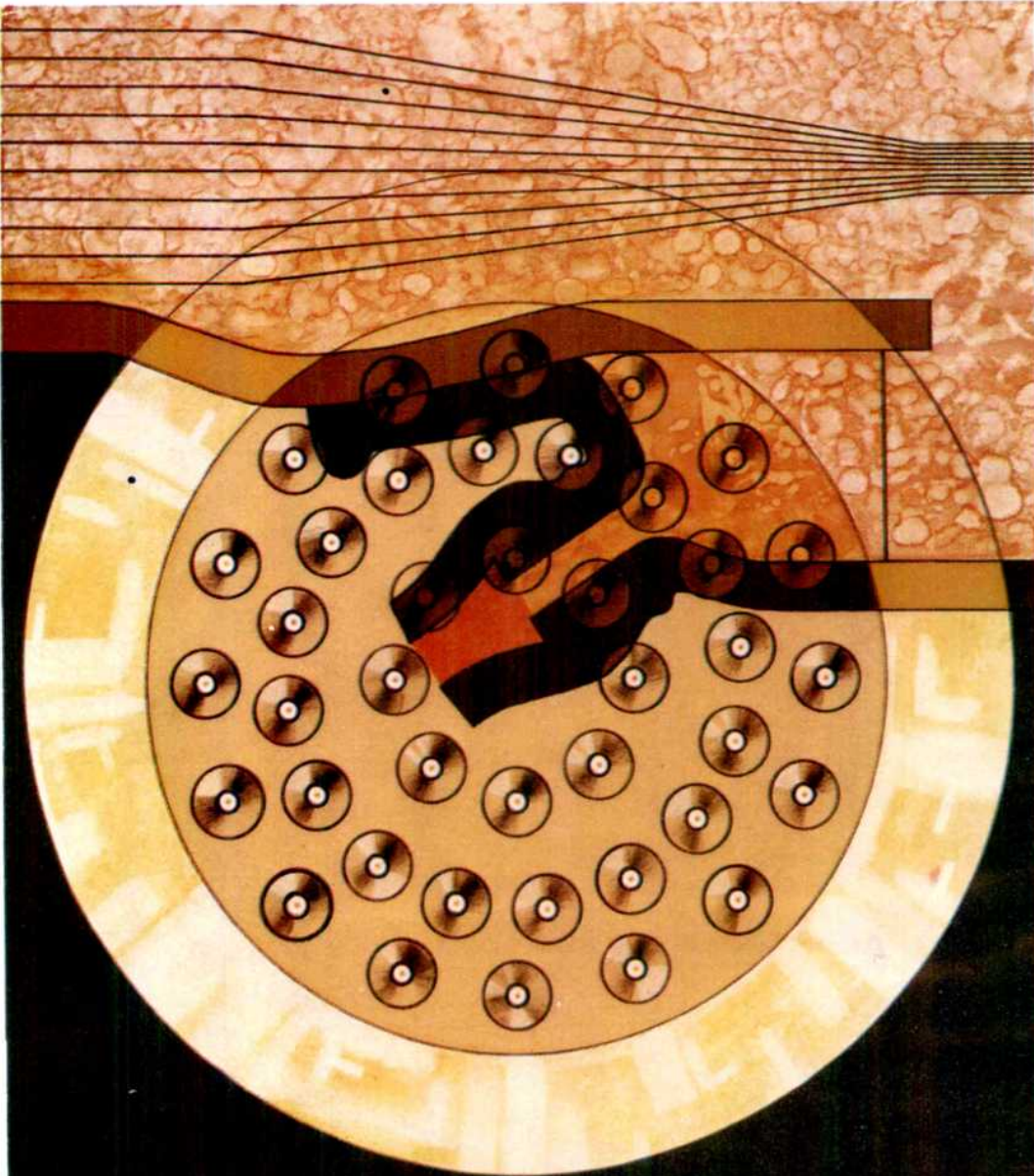
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Topical therapy of hyperendemic trachoma with rifampicin, oxytetracycline, or spiramycin eye ointments

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SUMMARY A double-blind stratified treatment trial was carried out on 108 patients with moderate to severe trachoma in a village in Southern Iran to assess the efficacy of topical therapy of 1% rifampicin eye ointment or 1% spiramycin eye ointment in comparison with 1% oxytetracycline eye ointment. A 6-week course of treatment with the antibiotics used twice daily produced a cure rate of 67% for rifampicin, 56% for oxytetracycline, and 64% for spiramycin when the upper tarsal conjunctiva was examined 1 week after completion of treatment. Seven months later the number of patients still free from active trachoma was reduced considerably. When the whole conjunctiva was examined, the cure rate for all 3 antibiotics was considerably lower than that obtained by examining the upper tarsus alone. The marked difference in response to treatment between the upper tarsus and the whole conjunctiva was due mainly to the presence of residual mild trachomatous inflammation in the upper fornix and the lower lid conjunctiva. The follow-up investigations revealed that this residual inflammation in the upper fornix and the lower lid is related to an increased risk of recurrence of inflammation in the whole conjunctiva, including the upper tarsal area. Microbiologically, after treatment with the antibiotics the isolation rate fell from 18-19% to 2-4%. Seven months later the isolation rate in the group treated with rifampicin or oxytetracycline remained low, whereas in the group treated with spiramycin this was raised to a level of 27%.

The result of this study indicates that under field conditions topical chemotherapy with rifampicin or oxytetracycline eye ointment twice daily for 6 weeks, though suboptimal, is beneficial in reducing the intensity of trachomatous inflammation and suppressing its transmission.

Hyperendemic trachoma continues to be a major cause of blindness in the rural populations of developing countries, especially those in Africa and Asia. Improvement in the standard of living and the level of rural public health would appear to be the ideal way to reduce and ultimately eradicate communicable ophthalmia, namely, trachoma and associated bacterial conjunctivitis (Jones, 1975). However, implementation of these measures is slow, expensive, and difficult and takes too long to be of considerable benefit to the present generation in danger of blindness due to these infections. Chemo-

therapy can be implemented rapidly and demands less resources. It is therefore used as an initial measure to prevent blindness in these countries.

The purpose of the present study was to assess in a double-blind stratified trial the efficacy of topical therapy of hyperendemic trachoma with rifampicin or spiramycin eye ointments in comparison with oxytetracycline eye ointment in a village in Southern Iran.

Subjects and methods

SELECTION OF PATIENTS

The child population of Tazian Paean, a village in the Bandar-Abbas area, Southern Iran, was ex-

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amined for signs of active trachoma. Children with moderate to severe grades of trachomatous conjunctival inflammation (Dawson *et al.*, 1975b) were included in this study.

CLINICAL EXAMINATION

Clinical signs observed with a Haag-Streit 900 slit-lamp were recorded on proformas by an extension of the scoring system used for the study of trachoma (Dawson *et al.*, 1975b). The clinical signs observed in different areas of the palpebral conjunctiva, namely upper tarsus (UT), upper fornix (UF), lower tarsus (LT), and lower fornix (LF), were graded on a 0-3 scale and recorded for each area separately. The intensity of inflammation in the upper tarsal area or the whole conjunctiva (WC) was calculated by a modified version of the system proposed by Dawson *et al.* (1975b) (Table 1).

PHOTOGRAPHIC DOCUMENTATION

Each area of the palpebral conjunctiva, namely, UT, UF, LT, and LF, and the limbus of each eye were photographed with a camera unit designed for this purpose (Jones and Sheen, in preparation) and Kodachrome II film.

The colour transparencies were subsequently examined in London, the clinical signs being quantified by 3 ophthalmologists following the method used during clinical examination. In case of disagreement among the observers transparencies were re-examined and compared with a standard set.

LABORATORY INVESTIGATIONS

Conjunctival swabbings collected from the upper tarsus, upper fornix, and the lower lid (LL) conjunctiva of the right and left eyes were placed together in a plastic capsule containing 2SP transport medium (Gordon *et al.*, 1969) with additional 3% fetal calf serum and stored in a liquid nitrogen refrigerator (-180°C) until transported to the

laboratory in London. Here they were stored at -70°C until the time of inoculation. The methods of culture in irradiated McCoy cells and the identification of the isolates have been described elsewhere (Darougar *et al.*, 1971).

RANDOM ALLOCATION

Children with active trachoma were divided into 3 groups according to a randomisation schedule stratified for age, sex, intensity of inflammation, and the number of children with active trachoma in each family.

MEDICATION

Each patient was treated with one of the 3 antibiotics, namely, rifampicin 1% eye ointment (supplied by Lepetit and Co. Ltd.), spiramycin (Rovamycin) 1% eye ointment (supplied by May and Baker Ltd.), or oxytetracycline 1% eye ointment (supplied by Pfizer Ltd.). The antibiotics were applied by experienced field technicians to the conjunctival sac twice daily for a period of 6 weeks. Those who received a total of less than 70 applications were excluded from this study. Of the patients included in the trial all except 2 received the maximum number of applications of ointment.

FOLLOW-UP INVESTIGATIONS

After initial clinical and laboratory examinations treatment was started in April 1974. The follow-up examinations with the collections of specimens were made at 1 week, 4 months, and 7 months after completion of treatment.

STATISTICAL ANALYSIS

Chi-square significance tests were used for a comparison of results.

Results

Initially 148 patients with moderate to severe trachoma (grades 3 or 4) in their whole conjunctiva were included in this trial. Of these, 40 were excluded, 22 due to inadequate treatment or follow-up and 18 because of the development of an adverse reaction to spiramycin. The allocation of the 108 remaining patients to the 3 treatment groups and their age and sex distribution are shown in Table 2.

Because of the close correlation observed between the results of screening transparencies and the clinical examination, and the high repeatability of scoring inflammatory changes by photography, the efficacy of treatment in this trial was assessed by scoring coded transparencies taken before and at intervals after the treatment.

When the upper tarsus alone was examined (the

Table 1 *Grades of intensity of active trachoma*

Intensity	Papillae score	Follicle score	
		Grade	Type*
0	No trachoma	0-3	0
1	Insignificant or inactive	0-3	4
2	Mild	1-2	1-3
3	Moderate	1-2	1-3
4	Severe	3	1-3

*Type of follicles: 0=no follicles, 1=follicles <0.5 mm in diameter, 2=follicles between 0.5 and 1 mm in diameter, 3=follicles >1 mm in diameter, 4=old follicles.

Table 2 Allocation of patients to various treatments, and their age and sex distribution

Treatment	No. of patients	Age				Sex (ratio) M/F
		0-1	2-4	5-9	10-14	
Rifampicin	45	4 (9%)	22 (49%)	17 (38%)	2 (4%)	60/40
Oxytetracycline	41	4 (10%)	22 (54%)	14 (34%)	1 (2%)	54/46
Spiramycin	22*	6 (27%)	11 (50%)	5 (23%)	0	41/59

*Eighteen patients were excluded from the trial because of the development of an adverse reaction to spiramycin.

conventional method) 1 week after completion of treatment, the cure rate for rifampicin was 67% compared with 56% for oxytetracycline and 64% for spiramycin (Table 3 and Fig. 1). The beneficial effects of treatment with each of the 3 antibiotics were statistically significant ($P < 0.05$). The differences between the efficacy of these antibiotics were not statistically significant. At the follow-up examination 7 months later the number of patients who were still free from active trachoma was reduced to 36% for rifampicin compared with 32% for oxytetracycline and 27% for spiramycin (Table 3 and Fig. 1).

When the trachomatous inflammatory changes were assessed in the whole conjunctiva, the cure rate for all 3 antibiotics was considerably lower than that obtained by examining the upper tarsus alone (Table 4 and Fig. 2). When the whole conjunctiva was examined 1 week after completion of treatment, the cure rate for rifampicin was 38% compared with 27% for oxytetracycline and 18%

Table 3 Number of patients cured examining the upper tarsal conjunctiva alone at various times after treatment

Type of treatment	No. of patients	No. cured		
		1 week	4 months	7 months
Rifampicin	45	30 (67%)	22 (49%)	16 (36%)
Oxytetracycline	41	23 (56%)	15 (37%)	13 (32%)
Spiramycin	22	14 (64%)	8 (36%)	6 (27%)

for spiramycin (Table 4 and Fig. 2). In the second follow-up 4 months later the number of patients still free from trachoma in the rifampicin group (40%) was higher than those treated with oxytetracycline (20%) or spiramycin (14%). This difference reaches statistical significance at a level of 5% ($P < 0.05$). However, this advantage of rifampicin was no longer significant at the third follow-up examination 7 months later.

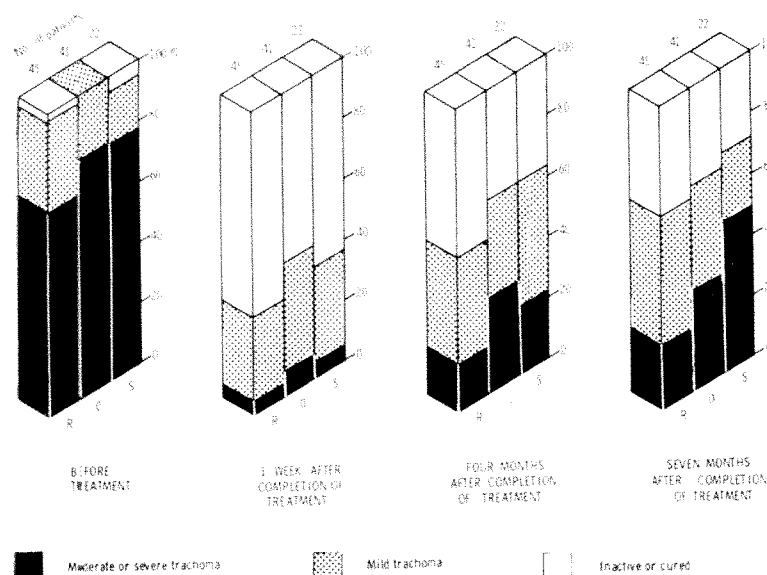


Fig. 1 Changes in the grades of intensity of trachoma in the upper tarsal conjunctiva after treatment with rifampicin (R), oxytetracycline (O), and spiramycin (S)

Fig. 2 Changes in the grades of intensity of trachoma in the whole conjunctiva after treatment with rifampicin (R), oxytetracycline (O), and spiramycin (S)

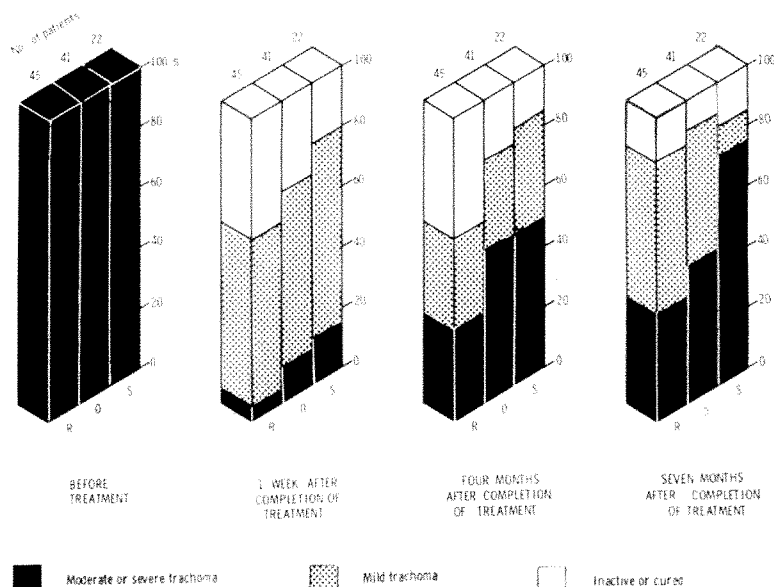


Table 4 Number of patients cured examining the whole conjunctiva at various times after treatment

Type of treatment	No. of patients	No. cured		
		1 week	4 months	7 months
Rifampicin	45	17 (38%)	18 (40%)	7 (16%)
Oxytetracycline	41	11 (27%)	8 (20%)	4 (10%)
Spiramycin	22	4 (18%)	3 (14%)	4 (18%)

In those patients who were not cured, the intensity of inflammatory changes in the upper tarsus as well as the whole conjunctiva was markedly reduced after the treatment with the 3 antibiotics (Figs. 1 and 2). The number of patients with grades 3 and 4 fell to 4% after treatment with rifampicin compared with 12% for oxytetracycline and 14% for spiramycin (Fig. 2). In the second follow-up 4 months later the intensity of inflammation in those patients who were not cured was significantly less with rifampicin than with either of the other 2 antibiotics (Figs. 1 and 2) ($P < 0.05$). This difference was not observed during the third follow-up.

The marked difference in responses to treatment between the upper tarsus and the whole conjunctiva was mainly due to the presence of residual mild trachomatous inflammation (grade 2) in the upper fornix and lower lid conjunctiva (Figs. 1 and 2). However, the follow-up studies in all groups treated with antibiotics showed that residual mild inflammation in the upper fornix and lower lid

conjunctiva is related to an increased risk of recrudescence of inflammation in the whole conjunctiva, including the upper tarsal area (Table 5).

No marked differences in response to treatment were observed between different age groups except in babies under 1 year old, who showed a poor response to treatment. There was no significant difference between males and females in response to treatment.

Microbiologically between 18 and 19% of patients allocated to each treatment group were positive for

Table 5 Number of recurrences and/or reinfections in 108 patients with or without inflammatory changes in their upper tarsus (UT) or the rest of their conjunctiva; upper fornix, and lower lid (UF+LL) after treatment with antibiotics

Group	1 week after treatment	No. of patients	7 months after treatment		
			No. of recurrences/ reinfections (UT + UF + LL)		
	Grade of inflammation		Mild	Moderate severe	Total
1	{ UT = inactive UF + LL = inactive	32	12	12*	24 (75%)
2	{ UT = inactive** UF + LL = mild to severe	35	7	25*	32 (91%)
3	{ UT = mild to severe** UF + LL = mild to severe	41	16	21*	37 (90%)

*The difference between group 1 and groups 2 and 3 combined is statistically significant at a level of 5% ($P < 0.05$). **Figs. 1 and 2.

Table 6 Number of positive cultures for *C. trachomatis* before and after chemotherapy

Type of treatment	No. of patients	No. of positives			
		Before treatment	After treatment		
			1 week	4 months	7 months
Rifampicin	45	8 (18%)	2 (4%)	0	1 (2%)
Oxytetracycline	41	8 (19%)	1 (2%)	2 (5%)	0
Spiramycin	22	4 (18%)	1 (4%)	1 (4%)	6 (27%)

Chlamydia trachomatis in irradiated McCoy cell culture (Table 6). Follow-up tests 1 week and 4 months after completion of treatment showed a considerable reduction in the number of positives in all 3 groups (Table 6). However, in the last follow-up 7 months later the isolation rate for the group treated with spiramycin was increased to a level of 27%, but no significant changes were observed in the positivity rates for those patients who were treated with rifampicin or oxytetracycline. This difference is significant ($P < 0.005$).

ADVERSE REACTIONS

Of 40 patients who were treated with spiramycin eye ointment 18 developed an adverse reaction 1-3 weeks after the start of their treatment. This consisted of watering, moderate discharge, moderate to severe swelling of lids associated with erythema, together with oedema and increased hyperaemia of the bulbar and palpebral conjunctiva. These symptoms and signs were increased with further applications of the ointment. However, after treatment was stopped the reaction subsided gradually in about a week.

Apart from slight discomfort and irritation, no other reaction was observed after applications of rifampicin or oxytetracycline eye ointments.

Discussion

In this trial preschool children with moderate to severe trachoma were included. Originally stratified randomisation for age, sex, grades of intensity of trachoma, and number of children with active trachoma in the family of patients produced a well-balanced distribution of patients in the 3 different treatment groups. However, because of the development of adverse reactions in patients treated with spiramycin eye ointment the distribution of patients in this group became somewhat different from the other 2 groups (Table 2).

The treatment trial was designed to test the efficacy of different topical drugs on hyperendemic

trachoma under field conditions. The eye ointments were applied twice daily. This schedule is more practical than thrice daily applications of ointment in the rural areas of Iran, where during the day adults, mostly accompanied by their young children, are working on their farms. During the 6-week course of treatment the total number of ointments applied was 84.

Examination of the upper tarsus alone 1 week after the completion of treatment showed a moderate cure rate for rifampicin, oxytetracycline, and spiramycin (56% to 67%). The intensity of disease was also reduced considerably in patients who were not cured. At the follow-up examination 7 months later the number of patients free from trachoma in all groups was halved (27% to 36%) and the intensity of disease increased markedly.

When the inflammatory changes of trachoma in the whole conjunctiva were assessed, the cure rate for all 3 antibiotics was markedly lower than that obtained by examining the upper tarsal conjunctiva alone. This difference was due to the presence of active but mild to moderate trachoma in the fornices of some of the patients with normal upper tarsal conjunctiva. In this group of patients (with normal upper tarsal conjunctiva but with active trachoma in their fornices) the rate of recurrence or recrudescence of moderate to severe trachoma was twice as high as in those who showed no active trachomatous inflammation in their whole conjunctiva, including the upper tarsus (Table 5).

In Tunisia treatment of hyperendemic trachoma with rifampicin or tetracycline ointments twice daily for a course of 10 weeks was shown to be beneficial in suppressing the disease but not in eradicating the infection (Dawson *et al.*, 1975a).

In London treatment of paratrachoma (inclusion conjunctivitis, TRIC punctate keratoconjunctivitis and trachoma) of sexually transmitted origin (Jones, 1975) with rifampicin eye ointment 3 times daily for 6 to 7 weeks was shown to eradicate the infection in 90% of patients (Darougar *et al.*, 1977). However, in the absence of apparent differences in the sensitivity of prototypes of TRIC agent serotypes as well as wild TRIC agent isolates to rifampicin, tetracyclines, and spiramycin (Trehan *et al.*, 1977) it can be argued that in the present study the lower cure rate obtained with rifampicin may be due to the suboptimal daily applications of the ointment or to a shorter course of treatment.

In this trial a control group was not included to assess the degree of natural decline in the intensity of trachoma with the lapse of time, increasing age, or seasonal variations. However, studies in Tunisia have shown that in children under the age of 6-7 with moderate to severe trachoma the intensity of

inflammatory changes in the conjunctiva remains fairly constant in a period of 1 year (Dawson *et al.*, 1975a). In the present study the majority of the patients included were children under the age of 7 with moderate to severe trachoma, and the course of follow-up was up to 7 months. Therefore it can be argued that the beneficial effect obtained in this trial is probably caused mainly by chemotherapy and not by the natural decline in the intensity of trachoma.

Immediately after completion of treatment the efficacy of topical therapy with rifampicin was very similar to that of oxytetracycline or spiramycin. In the second follow-up (4 months later) rifampicin appeared clinically to be superior to oxytetracycline or spiramycin by having fewer recurrences. In the last follow-up (7 months later) this difference was no longer present. At this time the cure rates for all 3 antibiotics were as low as 20% (whole conjunctiva). In this study the children in the trial were living with other untreated children and adults in the village, and no attempt was made to reduce the possibility of reinfections in these children by treating their families.

Microbiologically the chlamydial isolation rate before treatment was similar in the 3 groups (18–19%). At the last follow-up (7 months later) the isolation rate in groups treated with rifampicin or oxytetracycline remained low, whereas in the group treated with spiramycin it was increased to a level of 27%. The microbiological response to treatment with rifampicin or oxytetracycline obtained in this study is similar to those reported in trials in Tunisia (Dawson *et al.*, 1975a) and London (Darougar *et al.*, 1977).

In the group treated with spiramycin 18 patients developed moderate to severe adverse reactions. Bacterial cultures of samples of spiramycin ointments used in this study showed no growth. In London no adverse reaction was observed in patients with chlamydial, viral, or bacterial conjunctivitis who were treated with spiramycin eye ointment from the same batch. Although contact dermatitis due to spiramycin eye ointment has been reported previously (Hurwitz, 1959), the cause of this unusual reaction in children in Iran remains obscure.

In evaluating the effect of trachoma chemotherapy with rifampicin, oxytetracycline, or spiramycin we conclude that, though topical therapy with these antibiotics twice daily for 6 weeks is suboptimal, it may convert blinding trachoma in a community into a nonblinding disease (Dawson *et al.*, 1975b) if applied to the entire population.

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Clinical evaluation of clobetasone butyrate: a comparative study of its effects in postoperative inflammation and on intraocular pressure

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SUMMARY Clobetasone butyrate, a new corticosteroid with a high topical activity, has been compared with prednisolone phosphate and a placebo in the treatment of inflammation following cataract extraction. These 2 steroids were more effective in relieving postoperative inflammation than placebo ($P < 0.05$), though no obvious clinical differences between the 2 compounds emerged from this investigation. However, a single-blind comparative study against betamethasone phosphate in patients suspected of having steroid-induced glaucoma showed that, while betamethasone phosphate significantly raised intraocular pressure, clobetasone butyrate had only a minimal effect, and this difference was statistically significant ($P < 0.02$).

For more than 25 years corticosteroids applied locally have been used to suppress various types of ocular inflammation. However, although steroids have been used postoperatively to decrease inflammation following elective cataract extractions, their role remains controversial. Some ophthalmologists use them routinely, others when there is an unusual amount of inflammation, and a third group only rarely. Also among those who use this type of treatment there were wide variations in the frequency of application of the medication. However, one of the main disadvantages of steroid therapy is the production of steroid-induced glaucoma in certain individuals (Armaly, 1966), and this may be related either to the compound itself or to the concentration of 'available' steroid (Ramsell *et al.*, 1967).

The inflammation following surgical trauma provides a potential model for comparing the ability of steroids to reduce inflammation. Only 3 controlled studies have been published in this condition (Burge and Waltman, 1972; Mustakallio *et al.*, 1973; Corboy, 1976), and in the first 2 of these no difference in the resolution of the inflammation was found between steroid and placebo treated patients. However, Corboy found a statistically significant difference in favour of betamethasone phosphate used 5 times daily when compared with placebo.

Clobetasone butyrate, unlike betamethasone phosphate and prednisolone phosphate, is a steroid with a high cutaneous topical activity, as has been shown by its successful use in the treatment of inflammatory dermatoses (Munro and Wilson, 1975). It was postulated that because of this superior topical activity it might prove to be effective in the local treatment of external eye diseases. However, as it is also more lipid-soluble than either prednisolone phosphate or betamethasone phosphate it might therefore penetrate the epithelial layer of the cornea more readily and hence have a better therapeutic effect in intraocular inflammation.

The aims of the present investigation were to evaluate the anti-inflammatory activity of clobetasone butyrate and to assess its effect on intraocular pressure. A controlled study, with prednisolone phosphate and placebo as comparative groups, was therefore carried out in the treatment of postoperative inflammation. By including these 2 control groups it was hoped to determine whether this trial might provide a good model for the clinical evaluation of the steroids used in ophthalmology.

Patients and methods

CLINICAL STUDY

Fifty-seven patients who had uncomplicated intracapsular cataract extraction were selected for study. After operation they were treated twice daily for the

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first 4 days with chloramphenicol (0.5%) only. At the end of this treatment period they were randomly allocated to clobetasone butyrate (0.1%), prednisolone phosphate (0.5%), or a placebo preparation (vehicle only) in such a way that the clinical comparison was double-blind. All preparations were administered as 2 drops 4 times a day for the whole period of the study, and the chloramphenicol drops were also continued.

Patients were assessed by the same observer for postoperative inflammation on the 4th, 6th, and 10th (discharge) days and again 2 and 6 weeks after discharge. Inflammation was assessed by observation of the following factors: (a) Conjunctival injection was scored as absent (0), mild (1), moderate (2), or severe (3). Assessment was made for both bulbar (4 quadrants separately) and tarsal conjunctiva. (b) The degree of discomfort was ascertained by questioning the patients and was recorded on a 0 to 3 scale. (c) Complications were noted as either present (a score of 2) or absent (0), and these were: (i) striate keratitis, (ii) hyphaema, (iii) iritis. In addition, on the 10th postoperative day the surgeon (T. G. R.) gave his overall impression of the treatment as excellent, good, satisfactory, or poor.

INTRAOCULAR PRESSURE STUDY

Four patients who were suspected of having steroid-induced glaucoma were selected for a single-blind within-subject investigation comparing clobetasone butyrate with betamethasone phosphate. The intraocular pressure was measured, and in 2 of the 4 patients both eyes were studied. The patients were asked to instil betamethasone phosphate, 0.1% (treatment 1) 2 drops 4 times a day into the eye under investigation for a period of up to 6 weeks. During this time they were seen at two-weekly intervals, when their intraocular pressures were recorded. A 4-week period followed during which time no eye-drops were instilled and their intraocular pressures were allowed to return to their usual resting values. Then clobetasone butyrate, 0.1% (treatment 2) was instilled, 2 drops 4 times a day, for up to 6 weeks. Again intraocular pressures were measured at 2-weekly intervals. If, however, during the study the pressure rose more than 10 mm after 4 weeks the treatment was discontinued.

Results

CLINICAL STUDY

Fifty-seven patients (43 female, 14 male) between the ages of 49 and 90 years entered the study. Twenty patients (17 female, 3 male; age range 49 to 85 years) received clobetasone butyrate; 18 (13 female, 5 male; age range 66 to 90 years) received

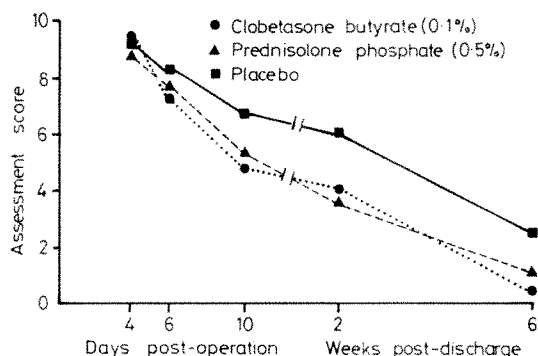


Fig. 1 Results of treatments determined by total assessment score with respect to time

prednisolone phosphate, and 19 (13 female, 6 male, age range 49 to 87 years) received a placebo. The groups were found to be matched with respect to age, sex, and initial severity of inflammation.

Fig. 1 shows the results of the 3 treatments as determined by the total assessment score with respect to time. Clobetasone butyrate and prednisolone phosphate were clinically more effective in relieving postoperative inflammation than the placebo, and the difference reached statistical significance (chi-squared test, $P < 0.05$) on the 10th postoperative day and 2 weeks after discharge. However, there was no obvious difference between the 2 steroids after these time periods, and no difference between any of the 3 preparations was seen 6 weeks after discharge.

These results were confirmed by the surgeon's overall impression on the 10th postoperative day (Table 1). Nine patients receiving clobetasone butyrate and 7 receiving prednisolone phosphate obtained an excellent or good response, whereas 17 patients receiving placebo had only a satisfactory or poor response (chi-squared test, $P < 0.05$).

INTRAOCULAR PRESSURE STUDY

This group of 4 patients (Table 2) were all intermediate steroid responders with pressure rises of between 6 and 16 mmHg following provocation with

Table 1 Surgeon's overall assessment of postoperative inflammation

Treatment	Excellent	Good	Satisfactory	Poor	Total
Clobetasone butyrate	1	8	7	4	20
Prednisolone phosphate	3	4	7	4	18
Placebo	1	1	5	12	19

Steroids superior to placebo: $P < 0.05$ (chi-squared test)

Table 2 Comparative effect of clobetasone butyrate and betamethasone phosphate on intraocular pressure

Patient no.	Age	Sex	Eye studied	Intraocular pressure (rise)							
				Betamethasone phosphate (q.d.s.)				Clobetasone butyrate (q.d.s.)			
				0	2 weeks	4 weeks	6 weeks	0	2 weeks	4 weeks	6 weeks
1	61	F	Right	19	24 (5)	30 (11)	—	22	22 (0)	21 (−1)	25 (3)
2	57	F	Right	18	19 (1)	23 (5)	25 (7)	17	17 (0)	21 (4)	20 (3)
3	68	M	Right	22	24 (2)	27 (5)	30 (8)	23	23 (0)	23 (0)	24 (1)
			Left	22	26 (4)	27 (5)	31 (9)	23	22 (−1)	22 (−1)	24 (1)
4	57	F	Right	18	23 (5)	28* (10)	—	19	18 (−1)	18 (−1)	19 (0)
			Left	18	23 (5)	29* (11)	—	21	20 (1)	22 (1)	21 (0)
Mean rise					4	8	8		0	1	1

* At 5 weeks

steroids. The mean rise in intraocular pressure over a period of 4 to 6 weeks with betamethasone phosphate (0.1%) was 8 mmHg (range 5 to 11 mmHg), whereas with clobetasone butyrate (0.1%) the mean rise over a similar period was only 1 mmHg (range 0 to 4 mmHg). This difference is statistically significant at 4 weeks (paired *t* test, $P < 0.02$).

Conclusion

In spite of the vast clinical experience and experimental work with locally applied corticosteroids the relative potencies of various steroids used in ophthalmology have not been evaluated from clinical investigations. Our work confirms that of Corboy (1976) and indicates that postoperative inflammation is a suitable model for the assessment of the potency of corticosteroids. Previous investigators who have come to the opposite conclusion have perhaps done so either because they used a weaker steroid such as hydrocortisone or did not apply the more potent agent sufficiently frequently.

Clobetasone butyrate is an effective steroid in reducing postoperative inflammation and is comparable in efficacy to prednisolone phosphate. It is of interest that our studies have shown that clobetasone butyrate has only a minimal effect on intraocular pressure when compared with betamethasone phosphate in patients known to experience steroid-

induced glaucoma. It is therefore of some significance that with clobetasone butyrate it has been possible to dissociate the adverse intraocular pressure effect from the advantageous anti-inflammatory effects, and thus we may well have a 'safer' steroid for use in ophthalmology.

The authors wish to thank Miss Susan Bristow for typing this paper.

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Crystalline stromal dystrophy: histochemistry and ultrastructure of the cornea

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SUMMARY A report of a woman in her fifties with Schnyder's crystalline stromal dystrophy is presented. There is no personal or family history of hypercholesterolaemia. A full thickness corneal disc was removed before grafting and examined by polarised light, histochemistry, and electron microscopy. Specific lipid histochemical methods showed deposits of cholesterol and cholesterol ester in the superficial stroma and in Bowman's membrane, but no triglyceride or free fatty acids were detected. Electron microscopy showed disruption of the superficial corneal stroma and Bowman's zone by cholesterol crystals and the presence of extracellular lamellated lipid droplets with a 4-4.5 nm periodicity. The epithelium, endothelium, and Descemet's membrane were virtually unaffected. The role of corneal grafting in crystalline stromal dystrophy is evaluated and the possible mechanisms of lipid accumulation in this disease are discussed.

Crystalline corneal dystrophy was first described by van Went and Wibaut in 1924 and by Schnyder in 1927 (Delleman and Winkelman, 1968). Many cases are familial with a dominant inheritance (Delleman and Winkelman, 1968), but there are accounts of isolated cases where a family history is not established—for example, patients reported by Bonnet *et al.* (1934) and Gillespie and Covelli (1963). The main features of the dystrophy (Delleman and Winkelman, 1968) consist of bilateral subepithelial corneal opacification situated immediately posterior to Bowman's membrane and central in position; numerous crystals are also seen in the affected central zone of the cornea, but there is no inflammation or irritation. A white girdle is often seen at the limbus, and some cases are associated with familial hyperlipoproteinaemia (Bron *et al.*, 1972). The condition is frequently present from early youth and rarely requires corneal grafting.

The present paper concerns a patient with crystalline stromal dystrophy without a firm family history. A full-thickness corneal graft was performed, which has allowed a more complete ultrastructural and histochemical examination of the cornea in this disease than has previously been published (Garner

and Tripathi, 1972; Babel *et al.*, 1973; Ghosh and McCulloch, 1977).

Case history

The patient is an unmarried woman now in her fifties who presented 10 years ago with progressive clouding of the central portion of both corneae (Fig. 1). Stromal clouding was also observed outside the central area of the cornea, but this is not well shown in Fig. 1. A marked arcus lipidalis was seen in both eyes. Apart from hirsuties no other clinical abnormality was detected. All living members of the patient's family were contacted, and none has diabetes mellitus or any corneal disorder.

CLINICAL INVESTIGATIONS

The patient's fasting blood sugar levels over the 10-year period were never above the normal range. Similarly, her fasting blood lipid levels were below 6.5 mmol/l on all occasions except one. In this instance the level was 7.2 mmol/l, but there is some doubt about whether it was a fasting level.

Fasting blood lipid levels were obtained from all living members of the patient's family (Table 1). All the sera were clear, but 1 fasting serum cholesterol level was somewhat raised; the triglyceride level in this case was normal. Two relatives had raised fasting triglyceride levels. The patient's

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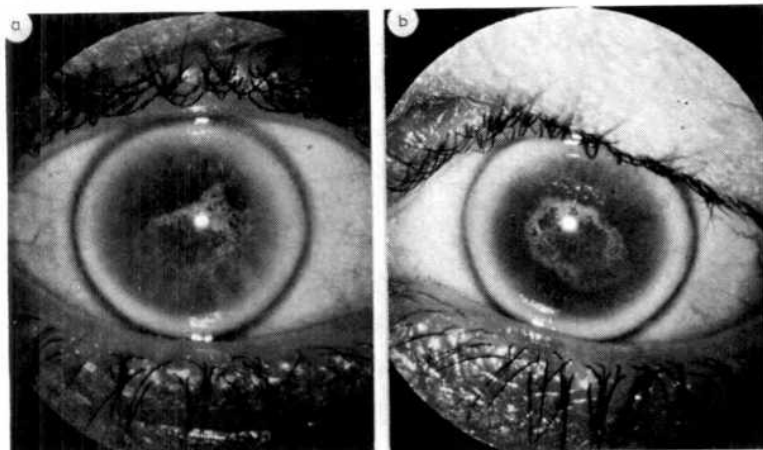


Fig. 1 Photographs of the patient's eye: (a) right and (b) left corneae show irregular central opacities and marked arcus lipidalis

Table 1 Fasting blood lipid levels of extant close relatives of the patient

	Fasting serum cholesterol in mmol/l (normal 4.0-8.2)	Fasting serum triglycerides in mmol/l (normal 0.79-1.69)
Brother	7.5	3.2
1st Cousin (mother's side)	5.7	0.79
1st Cousin (mother's side)	6.0	1.60
1st Cousin (mother's side)	4.2	1.31
1st Cousin (mother's side)	5.7	0.79
Aunt (father's side)	7.0	1.8
1st Cousin (father's side)	8.3	1.4

brother's level was markedly raised and her aunt's level minimally; in the aunt the cholesterol level was normal. These results show no association of the patient's crystalline stromal dystrophy with familial hyperlipoproteinaemia.

CORNEAL GRAFTING

Corneal grafting has been attempted in very few cases of crystalline stromal dystrophy, for, despite the obvious corneal lesion, reasonable vision is maintained for the greater part of the patient's life. It is difficult from the small number of grafts that have been performed, and from their brief follow-up, to assess the value of this procedure. In the present case the penetrating keratoplasty was successfully carried out in October 1977, as the patient was no longer able to continue her job. The operation was successful and uncomplicated, but 1 month after the operation there was evidence of subepithelial opacity in the cornea. Then the patient had an unfortunate fall in the street from which she sus-

tained epithelial abrasion of the graft, which healed only with the aid of a soft contact lens after readmission to hospital. There appears to be some permanent stromal damage 7 months after grafting.

PATHOLOGY

The 8 mm diameter full thickness corneal disc removed prior to grafting was fixed in 3% glutaraldehyde in 0.1 M cacodylate buffer for 4 hr. After 3 days' washing in 0.1 M cacodylate buffer containing 7.5% sucrose at pH 7.4 strips of cornea, including the central cloudy area, were taken for light microscopy, lipid histochemistry, and electron microscopy. Some strips were embedded in paraffin and 6 μ m sections cut and stained with haematoxylin and eosin, haematoxylin van Gieson, periodic acid Schiff, and diastase PAS. Tissue for electron microscopy was postfixed in Millonig's osmium tetroxide, dehydrated, stained with uranyl acetate, and embedded in Spurr resin. Sections 1 μ m thick were stained with 1% toluidine blue, and ultrathin sections were cut, stained with lead citrate, and examined in a Phillips 300 electron microscope.

Frozen sections of corneal strips were cut for lipid histochemistry. They were stained by the oil-red-O and perchloric acid naphthoquinone (PAN) method for cholesterol (Adams, 1961), the digitonide PAN technique (Schnabel, 1964), the lipase-calcium method for triglyceride (Adams *et al.*, 1966), and the Holcinger copper rubeanic acid method for free fatty acids (Adams, 1965). Unstained frozen sections were also prepared for examination in polarised light.

Results

HISTOLOGY OF THE CORNEA

The corneal epithelium was intact and there was

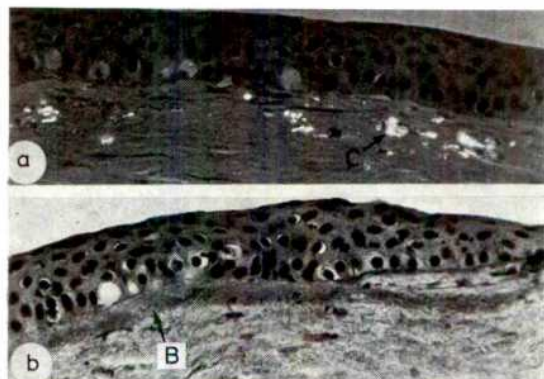


Fig. 2 Frozen section of cornea showing: (a) birefringent crystals (C) in the superficial corneal stroma. Polarised light counterstained with haematoxylin. $\times 255$. (b) High lipid content of Bowman's membrane (B) and lipid droplets in the stroma. Oil-red-O and haematoxylin. $\times 255$

no pannus. Bowman's membrane was continuous, but some disruption of the stroma was seen just deep to Bowman's membrane. No vascularisation or inflammation was observed within the corneal stroma, and neither Descemet's membrane nor the corneal endothelium showed any abnormality.

POLARISED LIGHT

Examination of frozen sections of the cornea by polarised light revealed focal clusters of needle-like crystals just deep to Bowman's membrane (Fig. 2). The crystals retained their needle-like shape at 37°C and 60°C , which suggests that their melting point was above 60°C . At 37°C birefringent droplets were seen in association with the crystals. These liquid crystalline droplets had a negative sign when viewed in polarised light and a first-order-red quartz plate.

LIPID HISTOCHEMISTRY

In frozen sections stained with oil-red-O Bowman's membrane was stained red or pink for much of its length, indicating a high lipid content (Fig. 2). Numerous small oil-red-O positive droplets were present throughout the stroma of the cornea but were concentrated particularly in the superficial areas of the stroma. Lipid droplets were not seen in Descemet's membrane. Sections stained by the perchloric acid naphthoquinone (PAN) and digitonide PAN methods for cholesterol and cholesterol esters showed that the lipid droplets within the stroma of the cornea were mainly cholesterol ester. No staining was seen with the lipase-calcium method for triglyceride or the copper-rubeanic acid method for free fatty acids.

ELECTRON MICROSCOPY

Epithelium. The epithelium was composed of layers of cuboidal cells with desmosomes (maculae adherentes) between adjacent cells. Occasional unattached cells were seen within the epithelium and appeared to be macrophages. The epithelial basement membrane was intact, but a few cellular processes extended into the superficial layers of Bowman's membrane.

Bowman's membrane. Bowman's membrane was recognised as a $10\text{--}12\text{ }\mu\text{m}$ wide layer of collagen bundles which were smaller and less well orientated than collagen in the stroma (Fig. 3). In the present case Bowman's membrane was considerably disrupted by the presence of numerous holes separating the collagen fibres. Many of the holes were roughly oblong with rounded corners and their long axes orientated parallel to the surface of the cornea. Some of the oblong holes were $1\text{ }\mu\text{m}$ or more in width. Vacuoles with circular or elliptical profiles were distributed fairly evenly throughout Bowman's membrane; many contained multilamellar bodies with a periodicity of $4\text{--}5\text{ nm}$.

Stroma. Aggregations of oblong-shaped spaces with rounded corners were seen in the superficial layers of the stroma. These spaces were larger than those seen in Bowman's membrane but were similar in shape. They corresponded in position to the crystalline structures seen in polarised light and were almost certainly the spaces left by the cholesterol crystals dissolved out of the tissue during preparation. Many of the spaces were long and narrow but others were short and wide (Fig. 3). Bands of collagen swept around the oblong holes, which were not bounded by membrane but only by the collagen fibrils. Multilamellar bodies were often closely associated with the geometrical holes (Fig. 4), but they were also seen throughout the stroma, always surrounded by collagen and exhibiting a $4\text{--}5\text{ nm}$ periodicity (Fig. 5). The oblong holes were observed only in the superficial regions of the stroma.

Endothelium and Descemet's membrane. Multilamellar bodies were seen in the stroma at the edge of Descemet's membrane but did not extend into it (Fig. 6). Descemet's membrane itself had some dark granular material deposited along its stromal aspect, but the rest of the membrane showed a diffuse grey electron density (Fig. 6). The endothelium was complete, and, although it was not optimally fixed, no structural abnormality was detected.

Discussion

The case of crystalline stromal dystrophy of the cornea presented here has no firm family history of

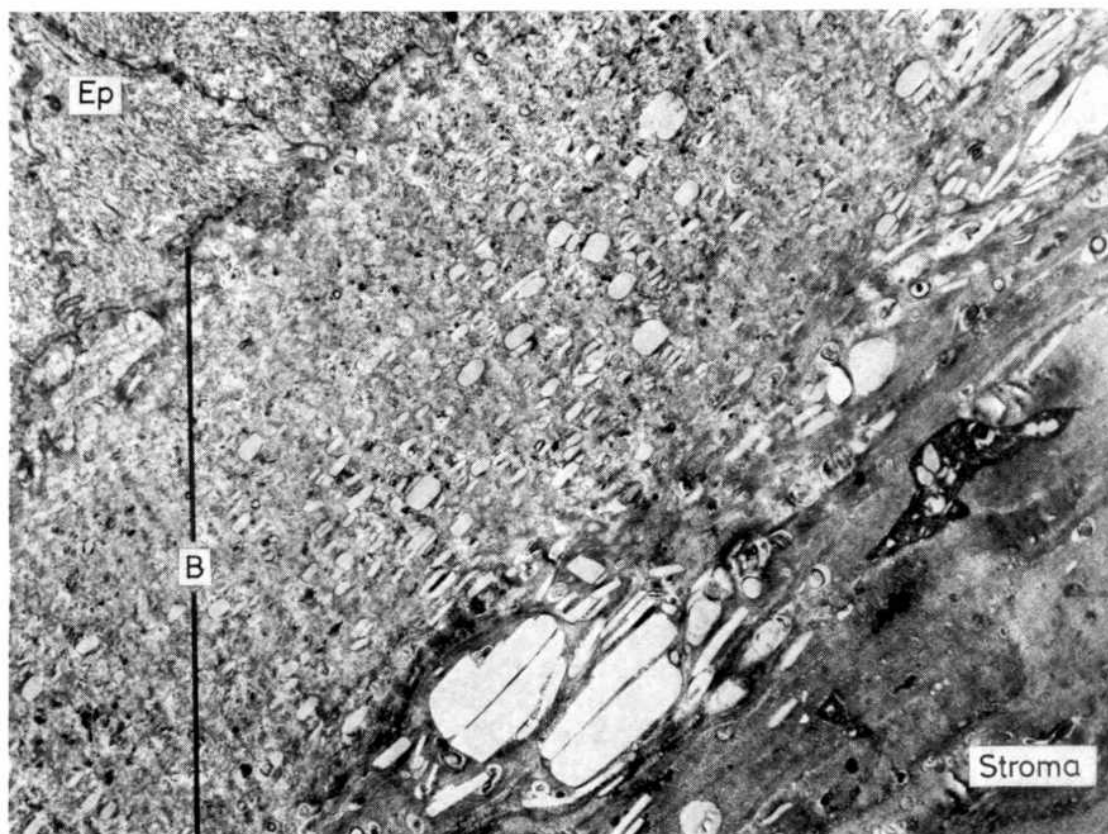


Fig. 3 Electron micrograph of Bowman's membrane (B) showing small oblong holes. The stroma contains larger angulated defects. Epithelium (Ep). $\times 6000$

corneal disease, nor is there evidence in the patient or surviving relatives of a familial disorder of lipid or carbohydrate metabolism. Some reports have stressed the high blood lipid levels found in patients with this disease, though unfortunately there is some doubt whether the levels were fasting, and often reports of blood sugar levels are missing. Standards of what constitutes hypercholesterolaemia have also changed over the years, which adds to the difficulty of interpretation. Nevertheless, Bron *et al.* (1972) reported very high levels of blood cholesterol and triglyceride in one patient with crystalline stromal dystrophy and moderately high levels of these lipids in a second patient. Two sisters in the same family were said to have hyperlipoproteinaemia. No figures for fasting blood sugars were given, and it is assumed that these were cases of true hyperlipoproteinaemia, though they were not classified by type. Bron *et al.* (1972) appear to be on less certain ground when they try to link the presence of the arcus lipidalis with the high blood

cholesterol even using Forsius's criteria (Forsius, 1954). On balance it seems unlikely that such a localised anomaly of corneal stroma bears any relationship to a systemic lipid disorder. Furthermore, it is probable that a proportion of the patients with crystalline stromal corneal dystrophy will have raised blood cholesterol values, as they are relatively common in the general population.

The distinction between the generalised hyperlipidaemia and a localised disorder of lipid metabolism is important. A high serum cholesterol is a contraindication to keratoplasty, as cholesterol accumulates much more rapidly in the injured cornea of cholesterol-fed rabbits (Rodger, 1971) and in the corneal grafts of hyperlipidaemic patients (Rodger and Sinclair, 1969). In the case of stromal corneal dystrophy, where the disorder of lipid metabolism appears to be localised and unrelated to any disorder of corneal corpuscles, it is too early to decide whether corneal grafting will be successful, as this procedure has been performed on only a few patients.

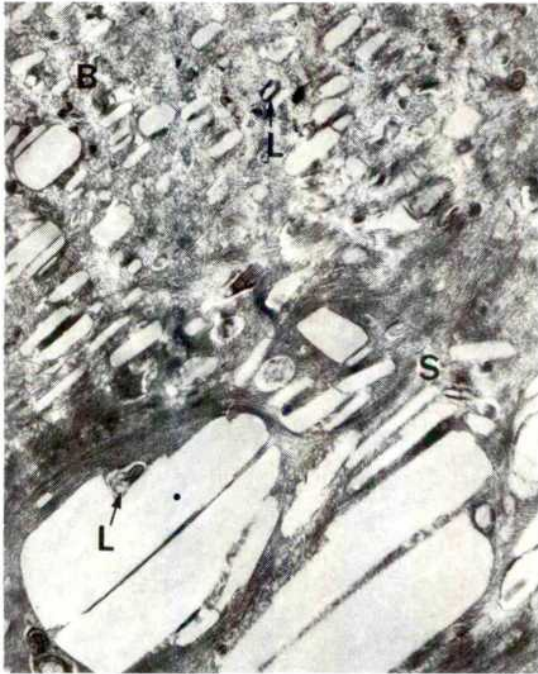


Fig. 4 Higher magnification of Fig. 3 showing disorganisation of collagen bands by the presence of angulated holes. Multilamellar bodies (L). Bowman's membrane (B). Stroma (S). $\times 10\,800$



Fig. 5 Multilamellar body in corneal stroma showing 4-4.5 nm periodicity. $\times 172\,000$

Delleman and Winkelman (1968) grafted 4 patients, 2 with lamellar and 2 with penetrating grafts. The latter type was more successful, but the deposition of crystals was observed in both grafts within a year, and in 1 patient subepithelial opacity was also observed. Garner and Tripathi (1972) investigated the cytological changes in a lamellar keratoplasty obtained from 1 of the patients treated by Bron *et al.* (1972). They reported crystal deposition in relation to the graft despite lipid clearing therapy, but no evidence of subepithelial thickening was noted as observed by Delleman and Winkelman (1968) and in the present case. Paufigue *et al.*, (1964) reported 1 successful lamellar keratoplasty, and Ehlers and Matthiessen (1973) performed 2 penetrating keratoplasties with apparently reasonable results, though neither has supplied subsequent data on the progress of the graft. From the small number of grafts performed in crystalline stromal dystrophy it seems that the value of keratoplasty is not yet established.

The availability in the present case of a full-thickness corneal disc for histochemical and electron microscope studies has made a more complete assessment of the extent of the corneal involvement possible. As with other cases (Bonnet *et al.*, 1934;

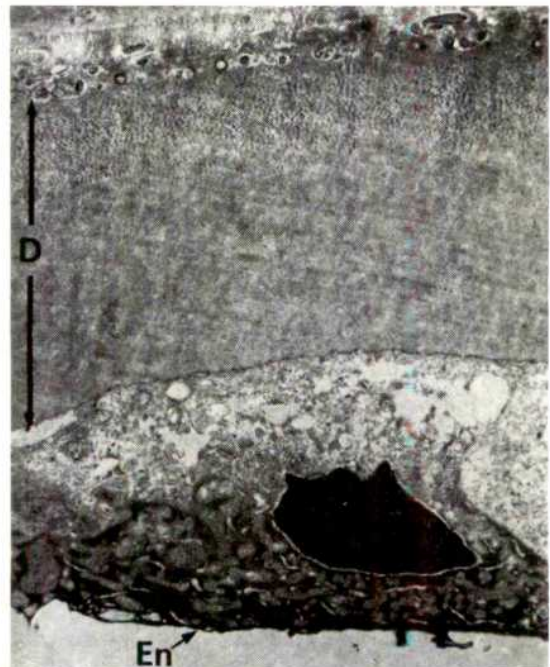


Fig. 6 Descemet's membrane (D) contains some granular material. Endothelium (En). $\times 5800$

Delleman and Winkelman, 1968; Garner and Tripathi, 1972; Ehlers and Matthiessen, 1973) the epithelium was unaffected. Malbran (1972), however, reported hyperplasia of the epithelium in 1 case, and Ghosh and McCulloch (1977) described foamy histiocytes in the epithelium of their case. Bowman's membrane is severely affected in most of the cases described. In the present case there were deposition of crystals and multilamellar bodies in the disrupted Bowman's membrane. Delleman and Winkelman (1968) described diffuse staining for lipids in Bowman's membrane similar to that seen in the present case. In the case described by Garner and Tripathi (1972), however, Bowman's membrane was destroyed except at the periphery of the cornea. The most severely disrupted region in the present case was in the superficial stroma just deep to Bowman's membrane, where the crystals were larger and the aggregates more compact. Lamellated bodies and lipid droplets were distributed throughout the stroma. Descemet's membrane and the endothelium appeared structurally normal apart from a vague, dark, granular material in part of Descemet's membrane.

There has been some dispute in the past about the identity of the birefringent crystals in the cornea, but the histochemical studies of Delleman and Winkelman (1978) and Garner and Tripathi (1972) suggest that they are cholesterol. The birefringent nature of the crystals and their high melting point in the present study also suggest that the crystals are cholesterol. This has been confirmed with the PAN method (Adams, 1961) for cholesterol, which is more specific than the Schultz method (Adams, 1965). Cholesterol esters form a major point of the lipid in the cornea in the present case, but no triglyceride was found by specific histochemical staining by the lipase calcium method (Adams *et al.*, 1966) despite the suggestion by Garner and Tripathi (1972) that the droplets were triglyceride.

The lipid droplets and crystals resemble in form those found in the subepithelial region of the cornea in hypercholesterolaemic rabbits (Rodger, 1971). Similar lipid droplets have been observed in atherosclerotic plaques (Weller, 1966; Weller, 1967). From their physical properties the birefringent droplets observed in polarised light appeared to correspond to the larger lamellated droplets. The 4.4–5 nm periodicity of the lamellated droplets suggests that they are formed from polar lipids, probably phospholipid mixed with cholesterol.

The origin of the cholesterol and cholesterol ester deposits in the cornea is most probably from the blood via the nutrient aqueous humour. However, the reason why there is local hypercholesterolemia of the cornea in crystalline stromal dystrophy is

unclear. As cholesterol and ester deposition can be induced in a similar site by hypercholesterolaemia, particularly where the cornea is scarred (Rodger, 1971), it may be due to a defect in the clearance of cholesterol from the cornea. Calcium salts similarly accumulate in the superficial stroma and Bowman's zone in other corneal lesions (Klintworth, 1977); this may also represent a defect in clearance of substances from this region of the cornea. Glycosaminoglycans within the corneal stroma may play a role in retaining cholesterol lipoproteins, as in the arterial wall, where dermatan sulphate appears to bind very low density lipoproteins and low density lipoproteins by ionic interaction (Iverius, 1973). The major sulphated glycosaminoglycan in the cornea, however, is keratan sulphate (Klintworth, 1977), and this differs from that in the arterial wall. In the absence of hypercholesterolaemia the deposition of cholesterol may be due to an abnormality in the composition of mucosubstances in the cornea itself. Histochemical stains on affected corneae have revealed no abnormality in the glycosaminoglycans (Malbran, 1972; Garner and Tripathi, 1972), but the defect may be more subtle than that detectable by histochemical techniques.

We thank Dr Olga Bayliss-High for her invaluable help with the histochemistry, and the staff of the neuropathology and electron microscope laboratories for their technical assistance. Mrs Olive Huber kindly typed the manuscript.

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Unilateral lattice dystrophy of the cornea

R. F. MEHTA

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SUMMARY Five cases of unilateral and 1 case of bilateral lattice dystrophy of the cornea in 1 family are reported. The diagnosis was made on the basis of the characteristic clinical appearance. The unilateral lesions were generally asymptomatic and required no treatment.

Lattice dystrophy of the cornea was first described by Biber (1890) and again by Haab (1899) and Dimmer (1899). It usually becomes evident towards the end of the first decade of life, though the characteristic changes have been observed earlier, at 2 years (Staatsbury, 1948), or later, in the third or fourth decades (Ramsay, 1957). Usually at about the 20th year the lesions become macroscopically obvious and classically occur bilaterally.

The dystrophy is characterised by the presence of opacification in a linear pattern in the superficial stroma, usually in the central region of the cornea. The corneal epithelium is spared, and therefore vision is good until the third or fourth decade. Corneal sensitivity is decreased when more severe changes occur. The stroma around these pathological changes remains clear until later in life. The opacities may eventually become confluent, forming a greyish white, central corneal leucoma. The clinical picture of corneal lattice dystrophy includes recurrent erosions, early decrease in vision due to irregular astigmatism, and later marked decrease in vision as the stromal lesions become denser. Lattice dystrophy of the cornea is hereditary and transmitted in an autosomal dominant manner.

Unilateral lattice dystrophy is a rare disease and no family with it has been reported. The first cases of unilateral lattice dystrophy were reported by Netchaiewa (1937) and subsequently by Hugonnier (1947). Ramsay (1957) reported 10 cases of lattice dystrophy, 1 of which was unilateral. Reshmi and English (1971) reported 1 case of unilateral lattice dystrophy in a 60-year-old woman. The most recent report of unilateral lattice dystrophy is of 6 isolated cases by Rabb *et al.* (1974).

This paper describes 5 cases of unilateral and 1 case of bilateral lattice dystrophy in 1 family. These unilateral cases have certain features which distin-

guish this entity from the classic form of bilateral lattice dystrophy.

Case histories

CASE 1

Subject II—2, Fig. 1. A 56-year-old white man was seen by a consultant ophthalmologist because his optician noticed a left corneal lesion and he could not improve his left visual acuity to more than 6/12 with corrective lenses. He was seen in the Eye Clinic, University of Sheffield, for second opinion. Examination revealed a unilateral lattice dystrophy involving the left cornea. Four years previously he had attended the Ophthalmic Casualty Department in Sheffield and was treated with antibiotic drops for left keratitis.

The lesion involving the left eye consisted of fine linear opacities, radiating from the central cornea (Figs. 2 and 3). The central cornea showed 1 nebular opacification. The limbal region remained clear.

The right eye had been asymptomatic and was normal on examination, with corrected visual acuity of 6/6, N5. There was no staining of the cornea with fluorescein or rose Bengal, and corneal sensation was normal.

His father suffered from bilateral corneal dystrophy and had been admitted twice in 1978 to Barnsley General Hospital for hypopyon ulcer of the right eye. His aunt lost the sight of her right eye owing to painless perforation of cornea, had the eye enucleated, and wears a prosthesis. His father's aunt had one eye enucleated, but the detailed history is not known. His mother died 26 years ago, and there was no history of eye trouble.

CASE 2

Subject I—1, Fig. 1. This 79-year-old white man, the father of case 1, was seen at Barnsley General Hospital with a history of gradually diminishing vision of both eyes and repeated attacks of sore eyes since the age of 50 years. Examination revealed

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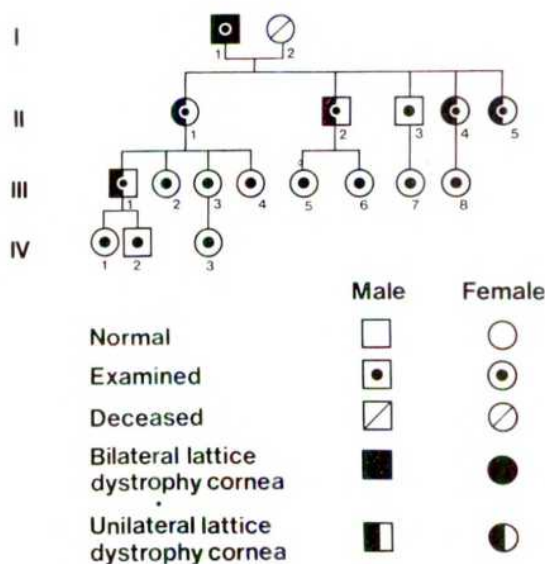


Fig. 1 Pedigree of a family

bilateral lattice dystrophy of the cornea, a right corneal ulcer with hypopyon, and some diminished sensation of the right cornea. The lesion involving the left cornea consisted of fine, linear opacities, radiating from the central cornea; numerous areas just adjacent to the central cornea showed nebular opacification. The limbal region remained clear. The corrected vision of the right eye was perception of light and of the left eye was 6/60. There were some cortical lens opacities involving the right eye more than the left.

The following patients were seen as part of the family study.

CASE 3

Subject II—1, Fig. 1. A 60-year-old white married woman gave a history of slightly blurred vision in the left eye recently; otherwise she was asymptomatic. The corrected vision in the right eye was 6/6, and the left eye was 6/9 part. Examination revealed lattice dystrophy of the left cornea. The right cornea was normal. There was no history of epithelial erosion or reduced corneal sensitivity, and the corneal sensation was normal in each eye.

CASE 4

Subject II—4, Fig. 1. A 49-year-old married white woman gave a history of measles at the age of 4 years followed by a sore left eye and left convergent squint, the vision being very poor since then. Examination revealed a moderate left convergent squint with glasses for near and distance, corrected vision right eye 6/6, left eye 6/60+1. The right

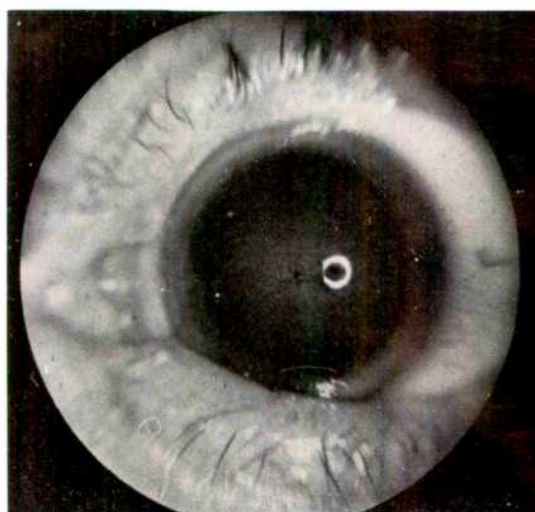


Fig. 2 Lattice dystrophy of the cornea, left eye (photograph by fundus camera)

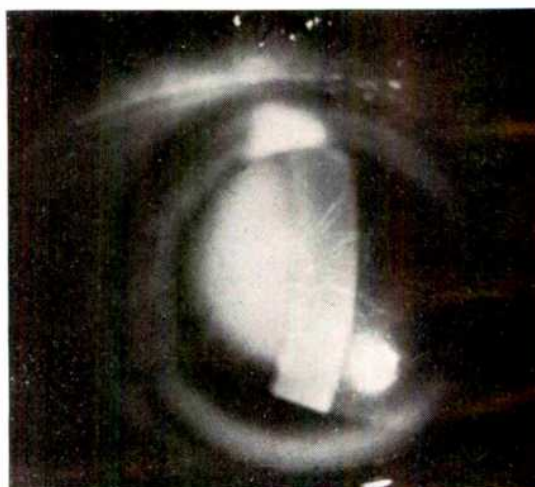


Fig. 3 Lattice dystrophy of the cornea, left eye (photograph by slit-lamp microscope camera)

cornea was normal with normal sensation and no staining. Left corneal examination revealed lattice dystrophy of the superficial stroma with central corneal scarring. The corneal sensation was normal, and there was no staining of the cornea.

CASE 5

Subject II—5, Fig. 1. A 43-year-old unmarried white woman gave a history of slightly blurred vision in her right eye. Her vision was right eye 6/9, left eye 6/6, not improved by glasses. Examination revealed corneal lattice dystrophy in the superficial stroma of the right eye with linear branching

opacities in the central stroma. There was no epithelial staining, and the corneal sensation was normal. The left cornea was normal.

CASE 6

Subject III—1, Fig. 1. A 38-year-old married white man gave a history of inability to see small print with his right eye; otherwise he was asymptomatic. His vision was right eye 6/6—2 and N5 with difficulty, left eye 6/5 and N5, not improved by glasses. Examination revealed lattice dystrophy of the right cornea.

The left cornea was normal. The corneal sensation was normal bilaterally and there was no staining of the cornea.

Subject II—3 (Fig. 1), subjects III—2, 3, 4, 5, 6, 7, and 8, and subjects IV—1, 2, 3 were also seen. Examination revealed no lattice dystrophy of the cornea and all had normal vision in both eyes. Corneal sensation was normal bilaterally and there was no corneal staining.

Discussion

The aetiology of lattice dystrophy is unknown and the pathology has been a matter for disagreement. There are basically 2 theories. The first is that lattice dystrophy constitutes a primary degeneration of stromal collagen fibres (Fuchs, 1925; Dark and Thomson, 1960). The second theory is that corneal nerves are primarily affected, with degeneration of the collagen fibres as the consequence of nutritional disturbance due to pathologic innervation (Pillat, 1922, 1923, Vrabec, 1957; Wolter and Henderson, 1963). Since 1967 many authors, including Klintworth (1967), Smith and Zimmerman (1968), and Meretoja (1972), have shown that deposition of amyloid is involved in lattice dystrophy of the cornea. The disease may therefore reflect a metabolic disturbance.

The 5 cases of unilateral lattice dystrophy reported here were either asymptomatic or had minimal symptoms, and all patients except one had 6/12 or better visual acuity in the affected eye. In 1 case the visual acuity was 6/60+1 in the affected eye, but there was a convergent squint in the affected eye and therefore the diminished vision in that eye may be due to partial amblyopia. The late onset, with minimal symptoms and preservation of relatively good vision in the affected eye, distinguishes it from the classic form of lattice dystrophy, but in family L described by Dark and Thomson (1960), visual disturbance and ocular discomfort began in the fourth decade or later. No pathological specimens of these unilateral lesions have been obtained.

Since unilateral lattice dystrophy is associated

with minimal symptoms, patients do not seek medical assistance, and many cases probably go undetected.

The family study is consistent with autosomal dominant transmission. The ages of the unaffected members range from 5 years to 36 years, and some of these may yet develop the condition.

I thank Mr N. L. McNeil, consultant ophthalmologist, who kindly allowed me to report his cases, and Mr A. Stanworth for his guidance.

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Rieger's anomaly: a 42-year follow-up

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SUMMARY A report is given on the follow-up examination of a patient 42 years after Rieger described her case as the first of a newly identified syndrome.

Rieger (1935) described two patients with striking anomalies of iris and angle. Each patient had glaucoma associated with hypoplasia of the anterior leaf of the iris, corectopia, and pseudopolyopia. There were iris adhesions both to the posterior surface of the cornea and to posterior embryotoxon, together with mesodermal tissue in the angle (Rieger, 1935). Later a number of systemic abnormalities were added, including oligo- or hypodontia, with abnormal enamel formation and maxillary hypoplasia (Rieger, 1941). Rieger called the condition dysgenesis mesodermalis cornae et iridis, to which his name was linked.

This report presents the findings for the first patient in Rieger's report who presented for re-examination 42 years later.

Case report

Our patient presented to the casualty department at Moorfields Eye Hospital in January 1977 with a 3-month history of gradual deterioration of vision in her right eye. Measurements of intraocular pressure had been limited to digital tonometry over the past 4 decades and had always been said to be 'normal'. Fifteen years ago she lost light perception in her left eye. She was on no medication.

OCULAR FINDINGS AT ORIGINAL PRESENTATION

At the age of several weeks she was noticed to have had 'changes' in both her eyes. When she was examined at the age of 10 (Rieger, 1935) her vision was 6/8 in each eye, intraocular pressures were raised in both eyes (between 40 and 50 in the left eye, and between 50 and 60 in the right), the right disc and field were normal, and the left disc showed

'flat' excavation and there was a corresponding nasal step in the left visual field.

The anterior segment showed striking changes which may be summarised as follows: The limbus was not well demarcated, and the change from sclera to cornea was very gradual. There were multiple areas of iris adherence to the posterior surface of the cornea at about 1.5 mm from the limbus, and the deeper corneal layers in that area were opacified. The iris itself appeared as a 'delicate membrane of dull brown colour' covered for the most part by yellowish grey tissue, which extended there from the angle. The usual iris structures (crypts, furrows, etc.) were absent. The pupils were abnormal, with corectopia, dyscoria in both eyes, and pseudopolyopia in the right (Figs. 1 and 2). The anterior chamber angles were open but mostly filled by homogeneous yellowish grey tissue. The remainder of the examination showed no abnormality apart from pigment deposits on the anterior capsule of the lenses.

The same year she underwent bilateral cyclo-dialyses. In addition a trephine operation was performed on her left eye.

OCULAR FINDINGS AT RE-PRESENTATION

The corrected visual acuity was 6/36 in the right eye and no light perception in the left. The intraocular pressures were 32 mmHg in the right eye and 68 mmHg in the left, together with epithelial oedema of the left cornea. The right optic disc was grossly cupped. There was no view of the posterior pole in the left eye because of a dense lens opacity. The right peripheral visual field was constricted above and nasally. In both eyes the anterior segment showed an indistinct limbus together with prominent embryotoxon, to which the iris stroma was adherent in a number of places. The iris was grossly deformed with corectopia, dyscoria, and symmetrical polyopia (Figs. 3 and 4). The abnormalities were similar to but more marked than they had been

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Fig. 1 A painting of the anterior segment of the right eye; patient aged 10. Corectopia and a small defect in the iris stroma at 11 o'clock. Iris adherent to the cornea in the 7 o'clock position. Indistinct limbus.

(Courtesy of the Editor, Albrecht von Graefes Archiv für Ophthalmologie)



Fig. 2 A painting of the anterior segment of the left eye, patient aged 10. Diagonal orientation of the ectopic pupil, no other stromal defect. Iris adherent to the cornea in the 7 and 1 o'clock positions

(Courtesy of the Editor, Albrecht von Graefes Archiv für Ophthalmologie)



Fig. 3 A painting of the anterior segment of the right eye, patient aged 52. The stromal defect in the 11 o'clock position is complete and much larger. Marked ectropion uveae with uniform radial striations of the iris stroma. The anterior synechiae are more extensive

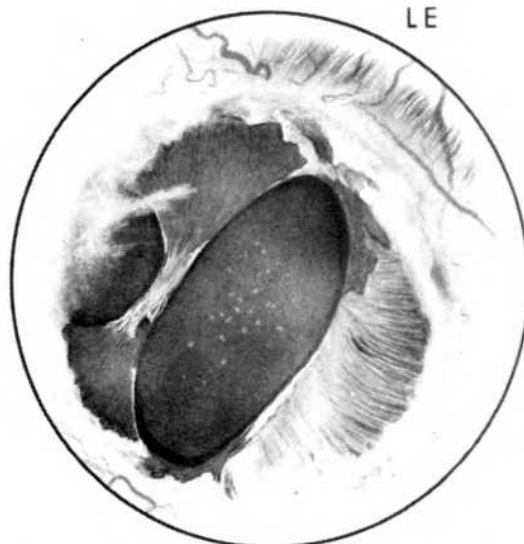


Fig. 4 A painting of the anterior segment of the left eye, patient aged 52. A new stromal defect in the 9.30 o'clock position, uniform radial striations. The anterior synechiae are more extensive.

42 years ago. There were concentric furrows in a uniformly light brown atrophic anterior leaf of the iris, ectropion uveae, and areas of frank stromal atrophy. In both eyes the anterior chamber angles were completely closed throughout their circumference. There were no abnormalities on systemic examination.

The patient's intraocular pressure was controlled with drops of guanethidine 1%, neutral adrenaline 0.25%, and pilocarpine 4%, and her visual field has not deteriorated further. The patient was not aware of any eye trouble in other members of her family. Her son was found on examination to have normal irides and angles.

Comment

This case report is remarkable for its time span and is also of historical interest. We agree with Rieger that this patient suffers from the anomaly that bears his name, because of the early onset, the bilateral involvement, and the typical appearances despite the absence both of a positive family history and of the systemic abnormalities commonly associated.

Two aspects of the management of this disorder deserve a comment. They are (1) progression of iris changes with Rieger's syndrome, and (2) the preservation of vision in eyes with uncontrolled glaucoma.

PROGRESSION

Rieger's anomaly has been described as a congenital deformity of iris morphology that does not progress (Alkemade, 1969). However, in a number of cases progression has been reported. Cross and Maumenee (1973), in a critical review, stated that progression when noted occurred before the end of the first decade, whereas other long-term follow-up reports suggesting lack of progression were for patients seen after the first decade. In our patient the slit-like defects in the irides which developed over the 42-year period are unlikely to have been caused by

the intraocular surgery or by iris stromal 'rarefaction' secondary to uncontrolled, raised intraocular pressure. We consider these changes to be the result of continuing dissolution of the iris.

MANAGEMENT

Alkemade (1969), in an extensive review of 163 patients with Rieger's syndrome, said that control of intraocular pressure was not easy to achieve. Patients did often not respond to traditional medical treatment, and a large number of operations had been employed in the past. Greater success was reported by Rice in a recent series. He controlled the glaucoma in 5 out of 6 eyes with Rieger's anomaly by means of goniotomy, though the same procedure failed to do so in 17 out of 19 eyes with the closely related syndrome of Axenfeld (Rice, 1977).

Our patient had uncontrolled glaucoma for an unknown but probably extensive period, but preserved useful vision in one eye for 52 years. This long-term visual prognosis should be borne in mind when surgical procedures are being considered for eyes with Rieger's syndrome.

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Indirect choroidal tears at the posterior pole: a fluorescein angiographic and perimetric study

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SUMMARY Retinal fluorescein angiographic and visual field studies were performed on 10 patients who had developed indirect choroidal tears, these procedures being repeated at intervals until the retinal disturbances stabilised. Fluorographic investigations revealed that a transient breakdown of the choroidoretinal barrier to fluorescein dye could be detected in cases investigated within 4 days of injury, and also that the late complication of neovascularisation, producing a serous maculopathy, may resolve and good central vision be retained without recourse to photocoagulation therapy. Patients who had visual field examinations performed within a few days of trauma were noted to have dense central scotomata, but some recovery occurred in most cases, although to a variable degree. Field defects away from fixation corresponded to an extent with areas of post-traumatic pigmentary retinopathy, but in some portions of retina with normal background appearances sensitivity was also noted to be reduced. Scotomata corresponding specifically to choroidal tears or nerve fibre bundle defects were not recorded. Improvement of visual acuity may be expected, except in cases where a choroidal tear has involved the fovea or progressive choroidal neovascularisation led to permanent macular damage.

Indirect choroidal tears at the posterior pole, commonly found in patients who have received severe concussive injuries to the eyeball, are now thought to arise from purely mechanical causes produced by forces generated at the time when a missile impacts against the globe (François and Bonnet, 1976). Splits develop in the choriocapillaris, Bruch's membrane, and sometimes in the pigment epithelium, permitting blood to extravasate into the choroid and the neural layers of the retina (Gass, 1967), but if the retinal pigment layer remains essentially intact a haematoma may form immediately underneath, giving rise to a haemorrhagic pigment detachment (Gitter *et al.*, 1968). These haemorrhages are subsequently absorbed. Pathological studies have shown that breaks in the choroid become invaded by connective tissue elements, and ruptures of the pigment layer are probably sealed by epithelial cells growing inwards from the edges of the tear (Duke-Elder and MacFaul, 1972). The question whether defects of the choroidoretinal barrier adjacent to the tear can be detected by

means of fluorescein angiographic investigations in the immediate post-traumatic period has, however, received little attention.

A variety of visual field changes have been described in cases noted to have indirect choroidal ruptures. Although scotomata relating to the typical pale, crescentic lesions detected on ophthalmoscopic examination were observed by Neame (1940), most investigators have noted central defects associated with post-traumatic maculopathies (Traquair, 1949; Harrington, 1964). Some workers identified sector field loss which they attributed to nerve fibre bundle disturbances (Harrington, 1964; Maberley and Carvounis, 1977), while others were unable to find any specific pattern of visual field impairment (Reed and Drance, 1972). Maberley and Carvounis (1977) stated that the field disturbances were usually greater than might be expected from signs detected on ophthalmoscopic examination and clearly did not relate to the crescentic lesions alone. Although central scotomata noted in the immediate post-traumatic period in patients developing concussive pigmentary maculopathies may become less dense and paracentral in position (Hart and Frank, 1975), there is some uncertainty whether field defects found in patients with choroidal tears alter with time.

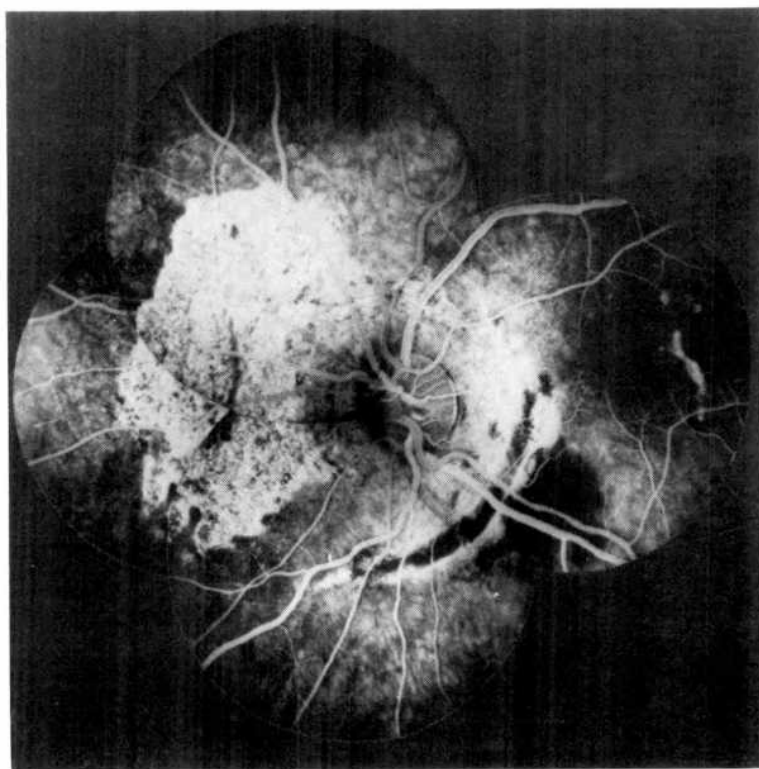
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Table 1 *Details of patients with choroidal tears*

Case No.	Sex	Age	Cause of injury	No. and position of tears	VA on initial examination	VA on final examination	Residual macular appearances	Duration of observation
1	M	34	Assault—iron bar	1 nasal to macula 1 involving macula	> 6/60	CF	Choroidal neovascular maculopathy	2 years
2	M	20	Assault—kicked	1 nasal to macula 1 involving macula	> 6/60	6/36	Choroidal neovascular maculopathy	3 years
3	F	22	Elbow	1 temporal to macula	CF	6/9	Pigmentation	4/12
4	M	19	Walked into projecting knob	1 nasal to macula	CF	6/6	Normal	8/12
5	M	18	Apple	1 inferior to disc 1 involving macula	CF	1/60	Tear bisecting macula	18/12
6	F	15	Airgun pellet	1 nasal to macula 1 temporal to macula	1/60	6/9	Cyst and pigmentation	4 years
7	F	28	Shuttlecock	1 nasal to macula	PL	6/18	Cyst	6/12
8	M	16	Hockey ball	1 inferior to macula	1/60	6/12	Pigmentation	4/12
9	M	38	Lump of metal	2 temporal to macula 1 involving macula	HM	HM	Tear bisecting macula	1 year
10	M	33	RTA	1 involving macula 1 inferior to disc	> 6/60	6/6	Pigmentation	2½ years

VA = Visual acuity. CF = counting fingers. HM = hand movements. PL = perception of light. RTA = road traffic accident.

Fig. 1 Case 5. Fluorescein angiogram left eye 5 weeks after trauma showing 2 choroidal tears, one below and temporal to the disc, the second bisecting the macula; retinal pigment epithelial disturbances have developed around the disc. VA 6/60



No studies on patients with indirect choroidal tears, in whom both sequential fluorescein angiographic and visual field investigations were performed, have to the best of our knowledge been reported. The findings of such a study form the basis of this communication.

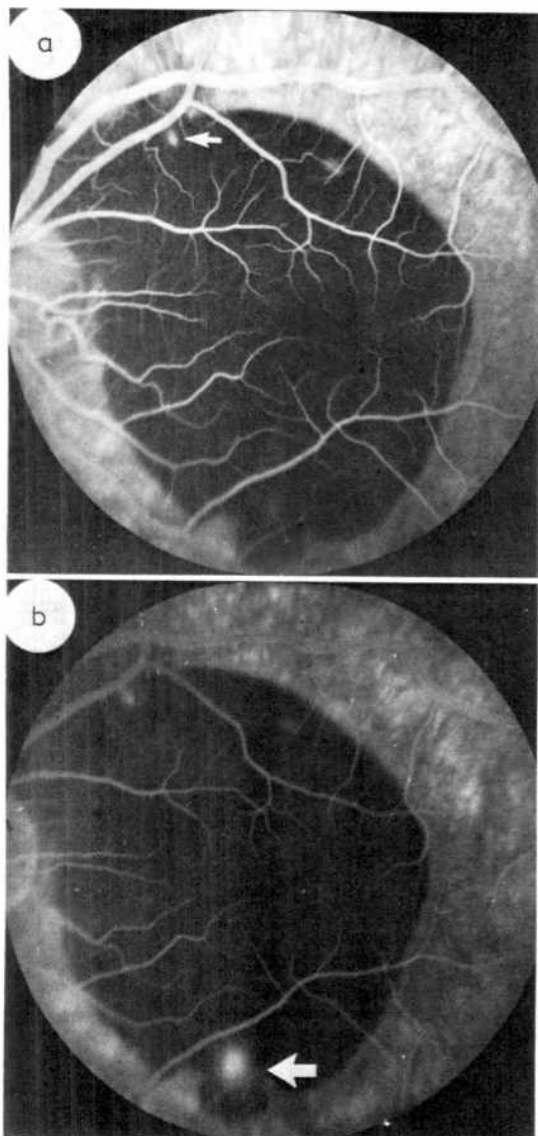


Fig. 2 Case 4. Fluorescein angiogram 2 days after trauma demonstrating (a) in the venous phase fluorescence from a tear appearing through the edge of a subretinal pigment epithelial haematoma above (small arrow); (b) in the residual phase, leakage of dye into the retina inferiorly (large arrow); fluorescence from the tear superiorly has faded. VA 6/60

Materials and methods

Patients attending hospital with a history of severe blunt mechanical nonpenetrating ocular injury, found on examination to have indirect choroidal tears at the posterior pole, were referred to our unit for further assessment. A full ocular examination was subsequently performed, which included evaluation of the corrected visual acuity, inspection of the fundus by indirect ophthalmoscopy followed by fluorescein angiographic and detailed Goldmann perimetric studies, both kinetic and static. Follow-up investigations were carried out until the retinal disturbances had stabilised. Only those patients with no

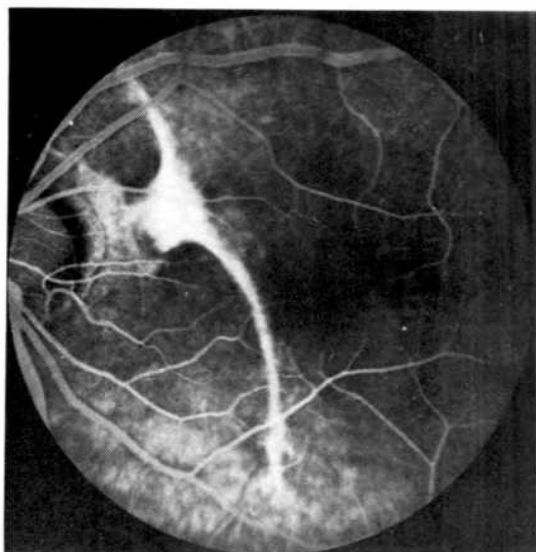


Fig. 3 Case 4. Fluorescein angiogram 8 months after trauma. The choroidal tear is now clearly defined. No leakage of dye into the retina has occurred. VA 6/6

evidence of pre-existing ocular disease who were able to co-operate fully with the programme and attended for follow-up investigations as required were retained in the series.

Results

Ten patients with indirect choroidal tears at the posterior pole, 7 male and 3 female in the age group 15–38 years, attended regularly for assessment over periods ranging from 4 months to 4 years. All had received uniocular injuries as a result of a wide variety of missiles impacting on the anterior half of the globe (Table 1), except case 10, who developed bilateral lesions after a road traffic accident, one eye

being so severely damaged that it was enucleated forthwith.

VISUAL ACUITY MEASUREMENTS

Although on initial examination central vision was noted to be severely depressed to 6/60 or less in all

patients, mainly due to impairment of retinal function, acuity eventually recovered to 6/18 or better in 6. Where it was observed that a choroidal tear had bisected the macula and extensive post-traumatic pigmentary changes appeared at the posterior pole, as in cases 5 (Fig. 1) and 9, no significant improvement in central vision occurred. In 2 cases, 1 and 2, visual acuity initially improved from less than 6/60 to 6/9 and 6/24 respectively and then deteriorated when subretinal neovascularisation and serous detachment of the macular developed (in case 1 4 months after injury and in case 2 18 months later). Neither the presence of a haemorrhagic pigment epithelial detachment involving the macular (seen in

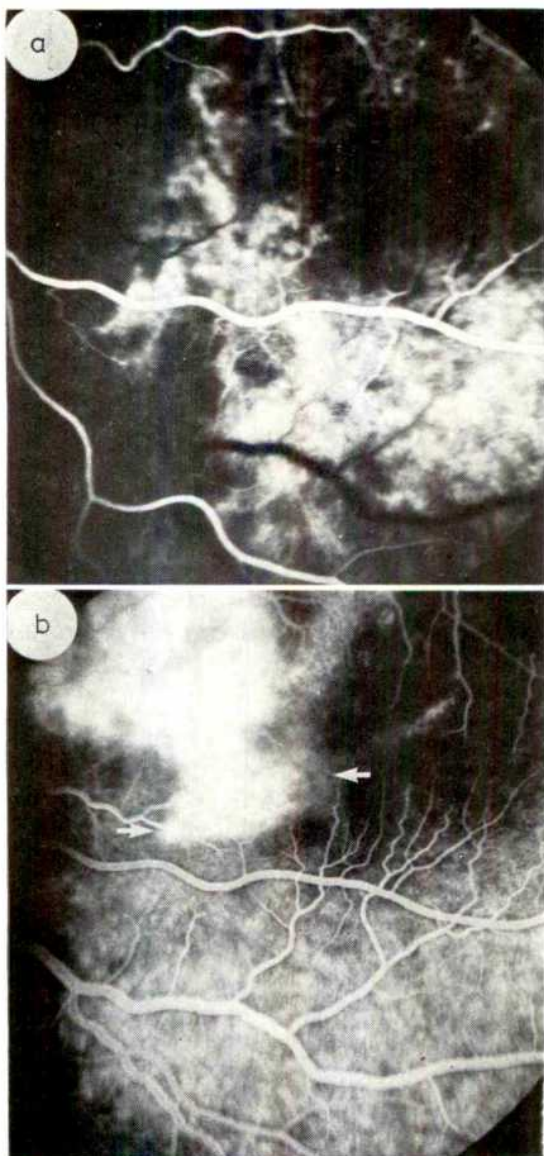


Fig. 4 Case 8. Fluorescein angiogram 4 days after trauma, showing (a) masking of the choroidal fluorescence between the disc and the macula in the arterial phase; (b) staining of retinal pigment epithelium and leakage of dye from a portion of the tear (arrows), late venous phase. VA 6/36

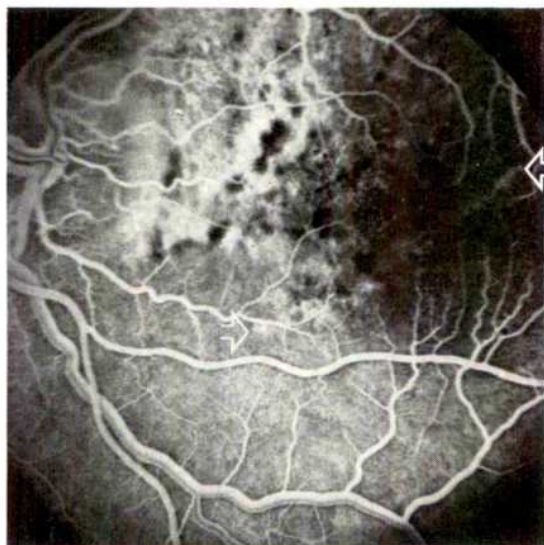


Fig. 5 Case 8. Fluorescein angiogram 7 days after trauma, venous phase. The extent of the tear is defined (arrows); no leakage of dye is apparent from this site and staining of the pigment epithelium limited to the region adjacent to the disc. VA 6/24

cases 3, 4, and 6) nor the location of choroidal tears, except when the fovea was involved, had any apparent bearing on the eventual degree of visual recovery. Visual acuity recovered to 6/12 or better in 4 patients who acquired post-traumatic macular holes or pigmentary maculopathies.

FLUORESCEIN ANGIOGRAPHIC STUDIES

Early changes

No disorders of the retinal vascular system were observed in the immediate post-traumatic period, and disturbances of the choroidal vessels appeared to be limited to the region of the tears themselves.

In cases 3 and 4, where any underlying tear was initially masked by a haemorrhagic pigment epithelial detachment, fluorescein studies performed 2 days after trauma showed leakage of dye into the neural layers of the retina at the margins of the haematoma (Fig. 2). These defects of the choroido-retinal barrier, subsequently found to be located close to the extremities of the rupture, resolved without further sequelae (Fig. 3). In case 8, examined

within 24 hours of trauma, retinal pallor was noted between the disc and the macula. Fluorescein angiographic studies 4 days after injury revealed marked staining of the retinal pigment epithelium in the opacified zone and leakage of dye from a small tear inferior to the macula (Fig. 4). Three days later barrier function had largely recovered (Fig. 5). Dye studies performed on case 1 5 days after injury, and on cases 5 and 7 within 6 weeks of injury, failed to show any leakage into the retina.

Late changes

Investigations performed 3 or more months after injury showed hyperfluorescence in the torn areas, normally maximal in the venous phase, but persisting

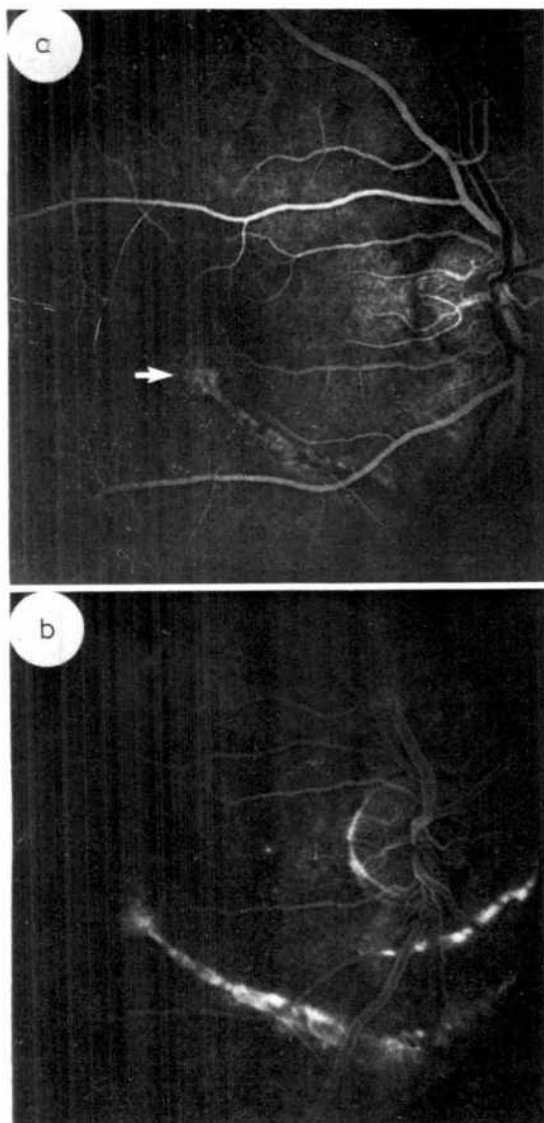


Fig. 6 Case 10. Fluorescein angiogram 4 months after injury, showing two choroidal ruptures with (a) new vessels outlined in the tear adjacent to the macula (arrow); (b) leakage of dye from this site. VA 6/18

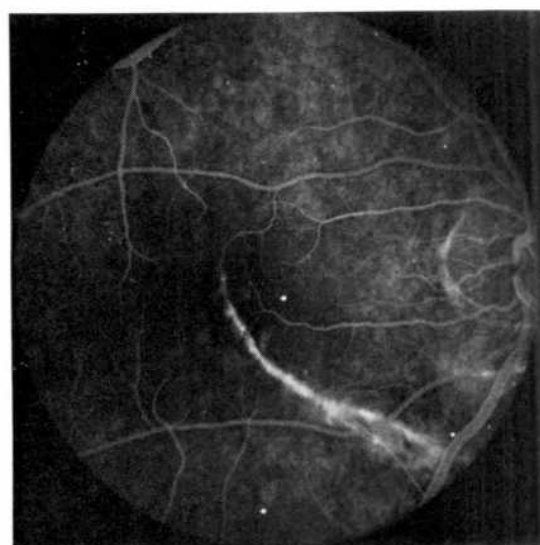


Fig. 7 Case 10. Fluorescein angiogram 6 months after trauma, demonstrating regression of new vessels. VA 6/9

into the residual phase (Figs. 1 and 3), and studies on 7 patients revealed no leakage of dye into the retinal tissues. In the only eye of case 10 visual acuity improved from counting fingers after trauma to 6/9 4 months later, but then deteriorated to 6/18. Macular oedema was observed, and fluorescein investigations revealed an area of choroidal neovascularisation arising from a portion of the tear adjacent to the macula, from which site a moderate leakage of dye occurred (Fig. 6). However, apart from a short dose of systemic steroids (prednisolone 15 mg daily for 1 month), no further treatment was given. The macular oedema resolved, and repeat fluorescein angiographic studies carried out 2 months later showed that the new vessels had regressed and the

choroidoretinal barrier now appeared intact (Fig. 7). This patient's visual acuity eventually recovered to 6/6. In two cases, 1 and 2, in whom progressive choroidal neovascularisation caused permanent macular disturbances, fluorescein angiographic studies showed the location and extent of the abnormal vessels (Fig. 8). New vessels temporal to the macula were photocoagulated in case 2, and

although visual acuity did not improve beyond 6/36 these vessels regressed and no further leakage of dye was subsequently detected.

Fluorescein angiographic studies also highlighted areas of pigmentary disturbance, the extent of which was not always easily identifiable on indirect ophthalmoscopy (Fig. 1).

VISUAL FIELD STUDIES

All patients seen soon after injury were noted to have dense central or centrocaecal scotomata, but retinal sensitivity at the posterior pole gradually recovered to a variable degree over a period of weeks or months (Fig. 9), deteriorating again only in those patients who developed serous maculopathies. In every case, however, residual defects adjacent to fixation could be found, which remained as permanent sequelae of the ocular trauma. Central scotomata tended to become smaller (cases 5 and 9) and less dense, as in cases 3, 4, 6, 7, and 8 (Fig. 10), and in case 10 small paracentral defects detectable by static perimetry alone were found at the final follow-up examination (Fig. 11).

We could not identify scotomata which could be specifically related solely to a choroidal tear, either on kinetic or static field testing, nor plot sector defects which might have indicated nerve fibre bundle lesions, although cases 5 and 10 showed barring of the blind spot immediately after trauma. Areas of reduced sensitivity were diffuse rather than focal and more widespread in cases where extensive post-traumatic retinal pigment epithelial clumping and atrophy had occurred. These changes had often developed at some distance from the tear (Figs. 1 and 12). Constriction of the peripheral fields was also noted in a few patients after injury, as in cases 5 and 10, but some expansion of the fields occurred over a period of time (Fig. 11).

Discussion

Reports on patients developing concussive maculopathies indicate that adolescents and young adult males form a high percentage of those seen with such injuries (François and Bonnet, 1976). This group runs a major risk of being involved in affrays, industrial accidents, and trauma related to sport. The sex and age pattern is similar for choroidal tears.

Although the spectrum of residual retinal damage is wide in patients who have acquired indirect choroidal ruptures at the posterior pole, permanent macular disturbances were detected on ophthalmoscopy in 9 out of 10 cases examined in this series. Eagling (1974) reported that central vision often recovered in cases developing post-traumatic maculopathies, though progress was slow, and might

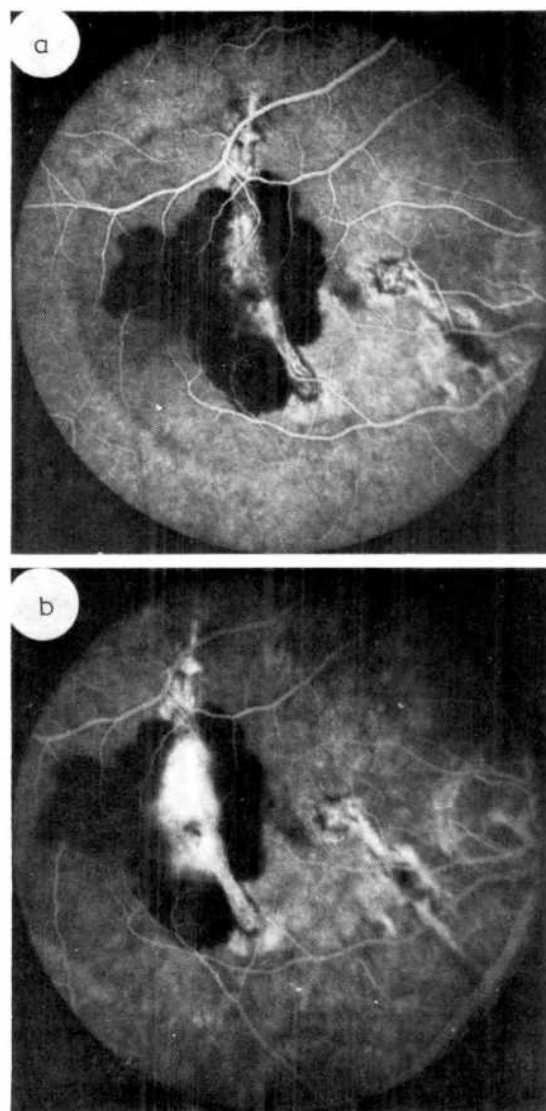


Fig. 8 Case 2. Fluorescein angiogram 18 months after trauma, showing (a) choroidal new vessels arising from a tear adjacent to the macula, with retinal haemorrhages temporally and nasally, and later (b) profuse leakage of dye from the central portion of the tear. VA 6/60

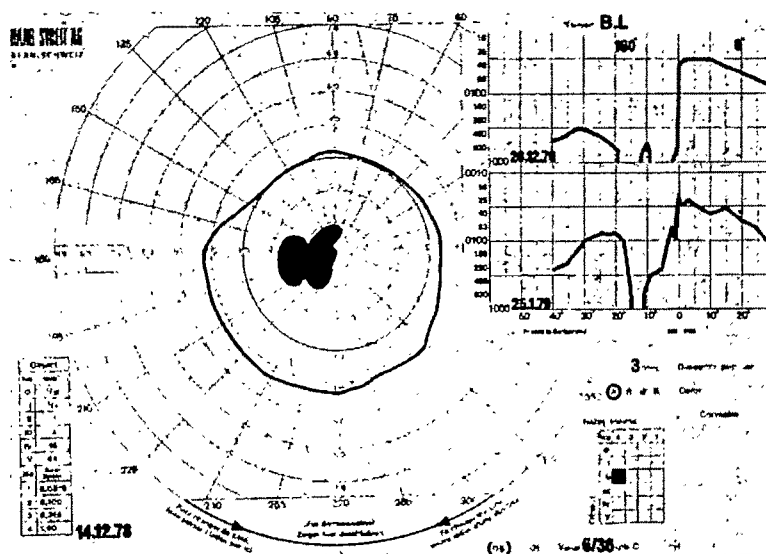


Fig. 9 Case 8. Visual field, left eye, 6 days after trauma. A centrocaecal scotoma is present. Static fields 20 and 48 days after injury (180-0° profile) showing recovery of retinal sensitivity in the central area

continue to improve for up to 6 months. François and Bonnet (1976) could not identify any factors on presentation which might be of prognostic value, except that if a choroidal tear involved the fovea the visual acuity remained impaired. Our investigations confirm the above findings.

The precise nature of the early disturbances which develop in the retinal pigment epithelium adjacent to indirect choroidal tears is poorly understood, as few eyes have been studied histologically soon after the traumatic event. Undoubtedly ruptures of the pigment epithelium may occur (Duke-Elder and

MacFaul, 1972), but Yanoff and Fine (1975) stated that, while Bruch's membrane and the choriocapillaris alone or the full thickness of the choroid is ruptured, the overlying retina is not usually found to be involved.

Fluorescein angiographic studies performed by us clearly demonstrated that disturbances of the choroidoretinal barrier can be detected in the immediate post-traumatic period, but that the leaks seal off within a few days. Retinal pigment epithelium has a marked ability to regenerate after a variety of injuries, including grade II traumatic retinal oedema

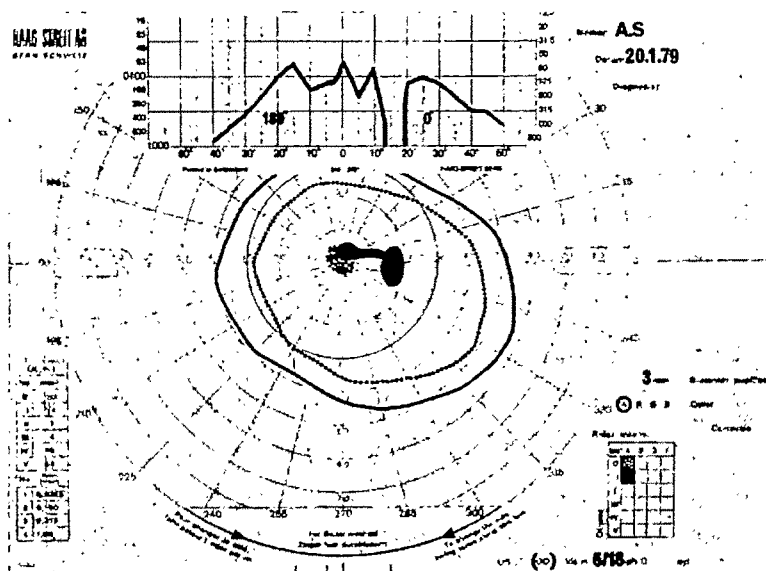
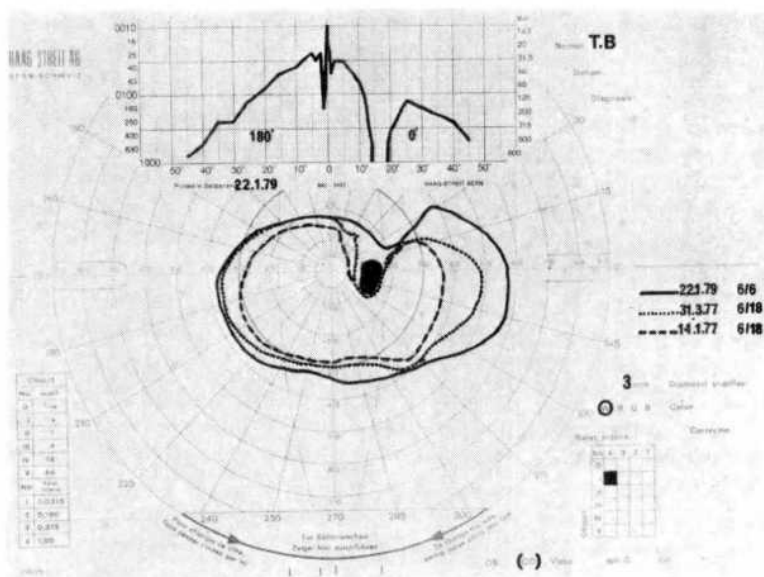


Fig. 10 Case 7. Kinetic and static (180-0° profile) field changes recorded 5 months after trauma to the right eye, demonstrating a centrocaecal defect

Fig. 11 Case 10. Showing progressive increase in size of the peripheral visual field 4 months, 6 months and 28 months after trauma. Static field (180-0° profile) demonstrates residual paracentral defects 28 months after injury

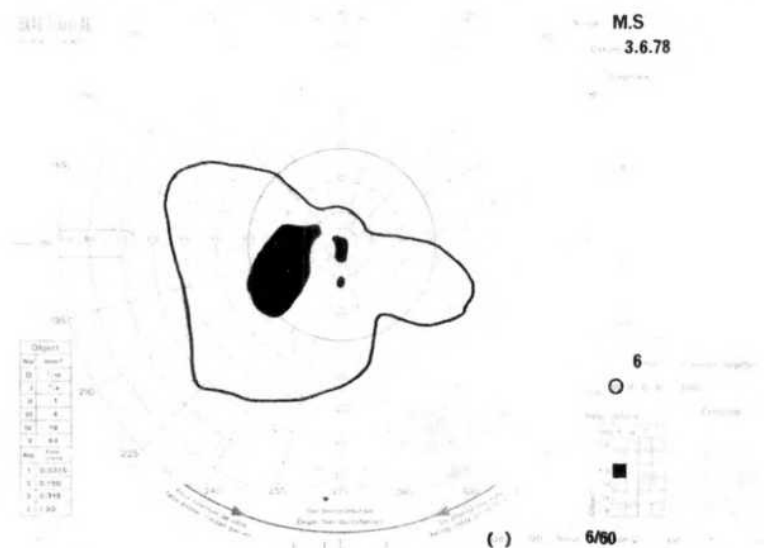


(Hart and Frank, 1975), but we are not aware of any previous reports describing similar changes in patients with choroidal tears.

Delayed breakdown of the choroidoretinal barrier associated with new vessels invading the retina through a choroidal rupture adjacent to the macula was initially reported by Gass (1970). Such disturbances may cause permanent macular changes with severe visual loss, though laser therapy has proved beneficial in some individuals (Fuller and Gitter, 1973). Two cases developing late macular changes have been reported in this series, but exami-

nation of our case records of patients with choroidal tears shows that less than 10% developed this complication. Late leakage of fluorescein dye into the retina following choroidal neovascularisation in a tear adjacent to the macula, which later subsided spontaneously, was described by Smith *et al.* (1974). The leak they detected was separated from the fovea by a zone of pigmentation, no therapy was instituted, and good vision was retained. On the basis of this report and our findings in case 10 it would seem advisable to withhold photocoagulation therapy in cases where delayed leaks occur, unless definitive

Fig. 12 Case 5. Dense central and paracentral scotomas are present 9 months after injury, which partially correspond to the retinal pigment epithelial disturbances noted on fluorescein angiography (see Fig. 1). Pupil dilated as result of traumatic mydriasis



evidence can be obtained of progressive choroidal neovascularisation. The role of systemic steroids in treating this condition must remain speculative.

Eagling (1974) suggested that central field analysis was helpful in determining the visual prognosis in patients who had received severe concussive injuries to the eyes, as areas of absolute scotomata, unless due to choroidal haematomata, showed no significant improvement with time. Our findings do not support this statement. All patients examined within a few days of injury in this series were noted to have a dense central scotoma. Although residual field defects were detected in every case seen up to 4 years after injury, on either static or kinetic perimetric testing, the majority of patients regained visual acuities of 6/18 or better.

Visual field defects away from the centrocaecal area were found to be nonspecific in type. The only association found in this study between lesions visible on ophthalmoscopy and field disturbances was that, in areas where post-traumatic pigmentary changes had developed, retinal sensitivity was reduced or absent. We agree with Maberley and Carvounis (1977) that field defects were often larger than might be expected from ophthalmoscopic examination of the fundus, and areas of retina with normal background appearances also showed some evidence of malfunction.

We did not detect in any of our cases definitive evidence of nerve fibre bundle defects. No signs of optic atrophy or changes in the nerve fibre light reflex could be found on red-free fundus photography. It is possible, however, that if a choroidal tear developed adjacent to the disc margin the blood supply to the optic nerve head might then be jeopardised and a sector defect produced. This would, in essence, be an incomplete avulsion of the optic nerve.

It is our impression that the principal disturbances leading to impairment of vision which occur in the retinae of patients presenting with choroidal tears are located in the photoreceptor outer segment and pigment epithelial layers. Such changes may involve large areas. Fragmentation of the photoreceptor outer segments has been noted to occur in primates after concussive injuries to the eyes, as a contre-coup response (Sipperley *et al.*, 1978). Similar changes have been reported in pigs after coup injuries, possibly as a result of mechanical shearing effects (Blight and Hart, 1977), and in these experiments regeneration of the photoreceptor outer segments was observed. If similar changes operate in man, an

improvement of the visual fields might well be explained on this basis.

We thank Mr N. L. Dallas, Mr W. Rich, and Mr D. Lyons, who referred patients to this department for assessment, Mr J. Morgan and the Department of Visual Aids, University of Bristol, for photographic services, and Mrs M. Roach for secretarial help.

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Glaucoma course

A course to present the practical aspects in the management of glaucoma, medical and surgical, will be held at the California School of Medicine, San Francisco, on 6–8 February 1980. Details from Extended Programs in Medical Education, University of California, 1308 Third Avenue, San Francisco, CA 94143, USA.

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The International Glaucoma Congress and the American Society of Contemporary Ophthalmology will hold their annual joint meeting 9–15 March 1980 in Orlando, Florida. Morning seminars will be devoted to glaucoma, cataract and intraocular lens, strabismus and paediatric ophthalmology, cornea and external diseases, contact lens, and oculoplastic surgery. In the afternoons tutorials and workshops for the practising ophthalmologist will be offered. Details from Dr John Bellows, American Society of Contemporary Ophthalmology, 6 North Michigan Avenue, Chicago, Illinois 60602, USA.

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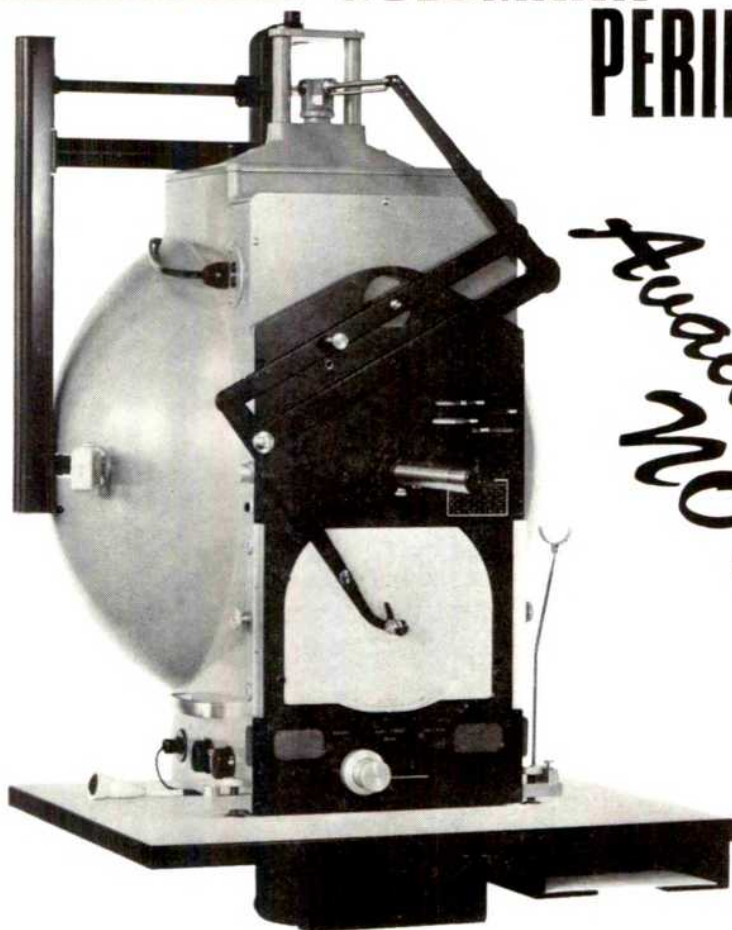
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Clinical electrophysiology

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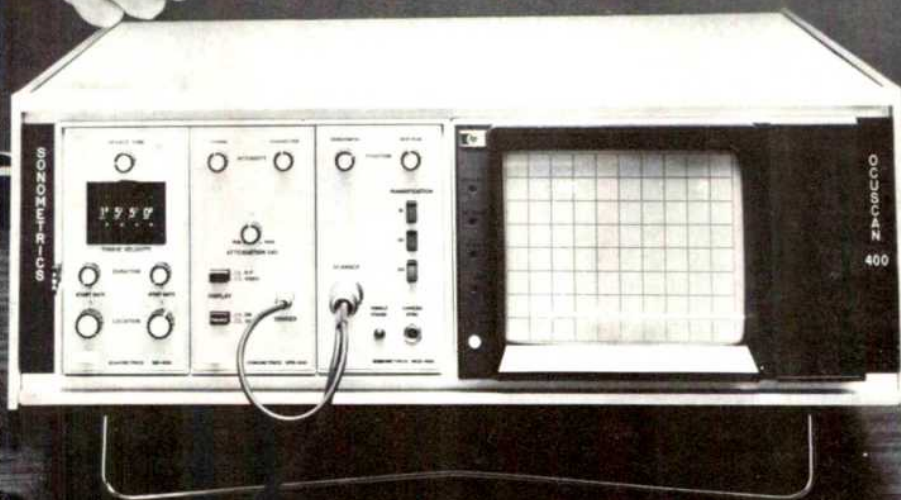
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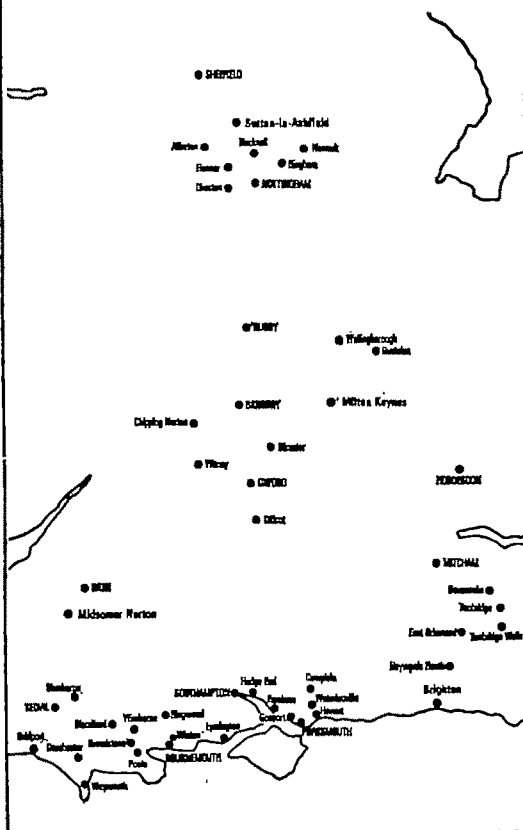
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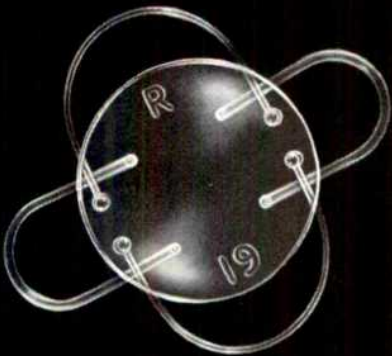
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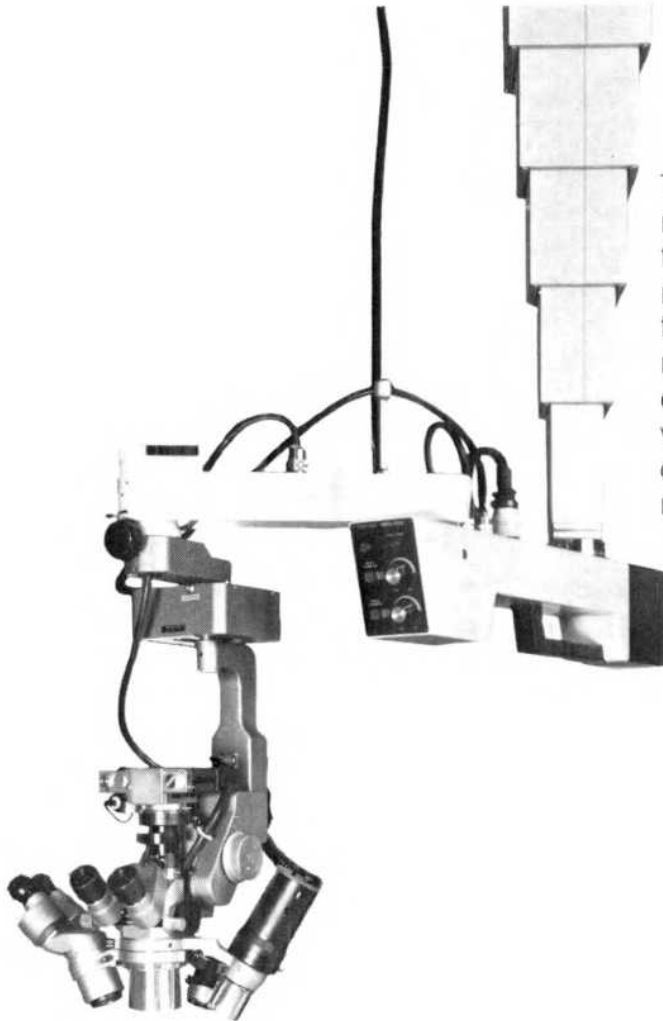
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Optic disc neovascularisation in diabetic retinopathy: I. A system for grading proliferation at the optic nerve head in patients with proliferative diabetic retinopathy

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SUMMARY An anatomical taxonomy for neovascular proliferation of the optic nerve head in patients with proliferative diabetic retinopathy is presented. The technique consists in comparing (A) number of involved quadrants, (B) calibre of vessels, (C) neovascular density, (D) neovascular area, (E) plane of proliferation, and (F) fluorescein angiographic findings. A similar taxonomy is used to describe fibrous tissue proliferation at the disc. With these criteria a series of standard photographs have been utilised in a numerical grading system. This system has proved useful in documenting the natural history and response to photocoagulation therapy for diabetic disc neovascularisation.

Diabetic retinopathy is often associated with a neovascular proliferation at the optic nerve head. This growth may be primarily vascular or fibrous or contain significant elements of both simultaneously. Previous methods of classifying these changes were incorporated in the Airlie House System¹ as well as others.²⁻⁷ Our more detailed classification of disc neovascularisation has facilitated its more precise documentation.

Material and Methods

All the patients with proliferative diabetic retinopathy seen in our laboratory had colour stereoscopic photographs taken of the optic disc. A Zeiss fundus camera and Kodachrome 25 colour film were used. Fluorescein angiography of the optic disc was also performed on each eye.

Disc proliferation was defined as any vascular or fibrous tissue emanating from the optic nerve head or located within 1 disc diameter of the disc margin. The vascular and fibrous elements were evaluated separately. Arbitrary criteria for a scale of relative importance were established. In this manner a scoring method was created to grade the prolifera-

tion in regard to the separate neovascular and fibrous changes.

The disc neovascularisation (NVD) was reported according to the following parameters:

A. The number of quadrants (1-4) of the optic disc in which neovascularisation could be identified (Figs. 1a-d).

B. The calibre of the new blood vessels. It was called stage I when the largest diameter of the new vessels was less than half the size of the first branch of the central retinal artery; stage II when the new vessel calibre was between the half size and less than full-size of that branch artery; and stage III when the new vessel's largest diameter was equal to or greater than that branch artery (Figs. 2a-c).

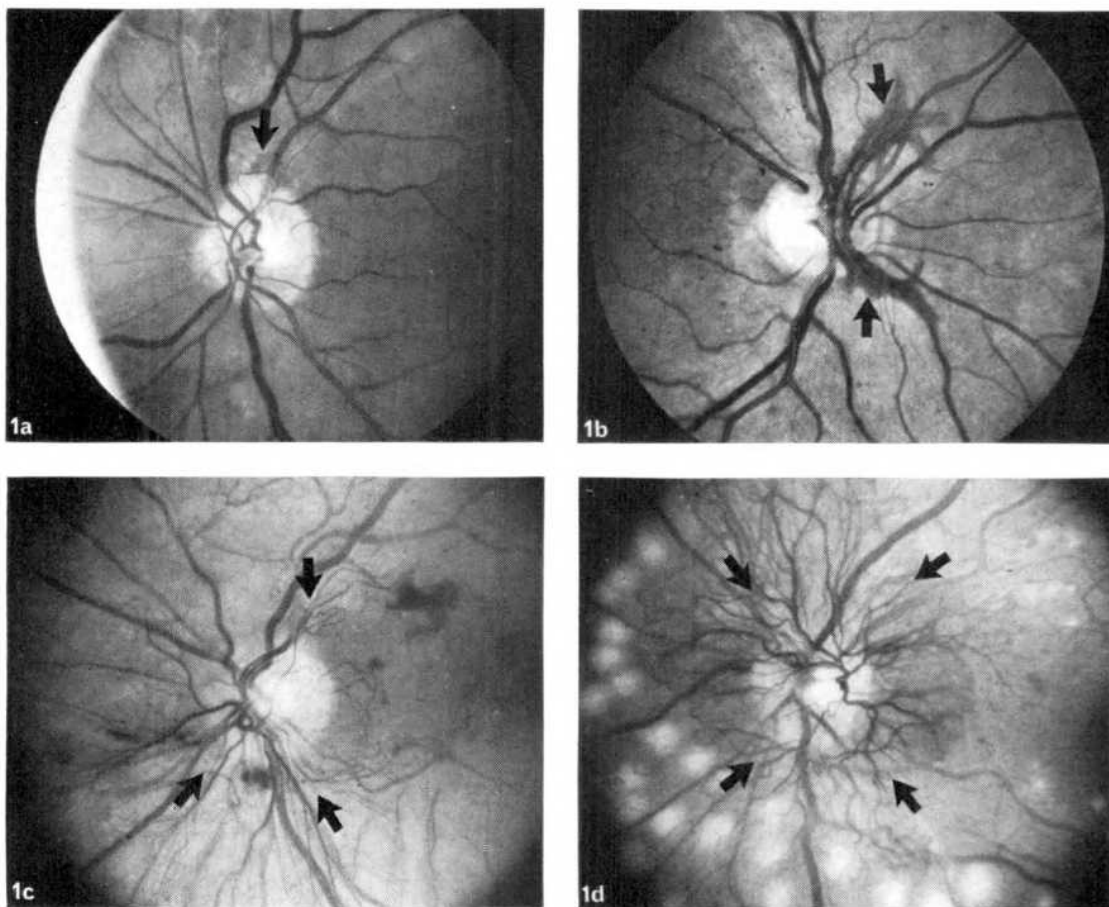
C. Neovascular density was evaluated in comparison to a series of standard photographs. Four standards were established as shown in Figs. 3a-d. The stage of density was determined according to the standard photograph it resembled most (stages I-IV).

D. Area of neovascularisation was determined by measuring disc diameters of NVD on the stereoscopic photographs. It was called stage I when the total area was up to 2 DD; stage II when it was up to 5 DD; stage III when it was up to 10 DD; and stage IV when the total area was more than 10 DD.

E. The plane of proliferation of the new vessels was also determined by examining the stereoscopic photographs. It was called stage I when there was

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Figs. 1a-d Illustrations to show number of quadrants involved with neovascularisation: 1a. Arrows point to neovascularisation in 1 quadrant. 1b. Neovascularisation involves 2 quadrants of the disc. 1c. Disc neovascularisation involves 3 quadrants of the disc. 1d. Neovascularisation involves all quadrants of the disc.

less than one-quarter disc diameter of elevation; stage II when the elevation was between one-quarter and 1 disc diameter; and stage III when the elevation was more than 1 disc diameter.

Fluorescein angiography was performed to demonstrate neovascular leakage. The dye leakage was recorded between 1 and 2 minutes after the injection, and was evaluated as stage 0, I, II, or III, depending on the degree of dye leakage; a series of the following standard angiographic photographs were used for reference (Figs. 4a-c).

The parameters examined were quite dissimilar, and the stage number associated with each parameter could not be used to interrelate the findings, since they measured different criteria. For this reason the above listed parameters A-F were given certain scores according to our previous observa-

tions since 1960 on the natural history of approximately 600 patients with NVD that were not treated. We had concluded that the most important clinical parameters were the plane of proliferation and the total area of proliferation (parameters D and E in our list), since these were the key findings associated with vitreous haemorrhage, fibrosis, and traction retinal detachment. Therefore each of these parameters received a score of 40 points toward the total score of 100. The other four parameters (A, B, C, F) received a score of 5 points each. Each stage within each of the A-F parameters received their points as follows:

$$\frac{\text{Total no. of points for parameter}}{\text{No. of stages composing the parameter}}$$

and the points were added to each other when

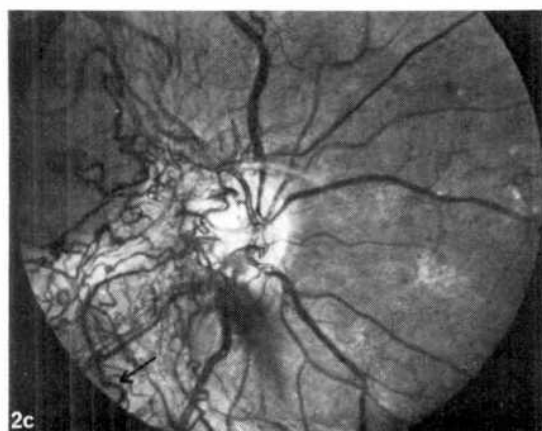
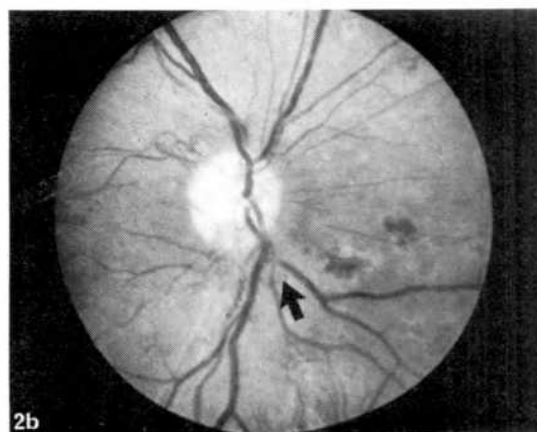


Fig 2a-c The largest vessel in the neovascular frond is graded for calibre in reference to the retinal arteriolar size as it crosses the optic disc margin; 2a. Calibre stage I showing neovascularisation less than one-half retinal arterial diameter at the disc margin. 2b. Calibre stage II showing largest vessels in neovascular frond equal to two-thirds diameter of retinal arteriole at disc margin. 2c. Calibre stage III showing largest vessels in neovascular frond are slightly greater than diameter of the retinal arteriole at the disc margin.

moving up to the next stages of each parameter:

Table 1 Point system of stages and parameters of NVD

Parameter	No. of points of stage in parameter				No. of maximal possible points of parameter
	I	II	III	IV	
A	1½	2½	3½	5	5
B	1½	3½	5	—	5
C	1½	2½	3½	5	5
D	10	20	30	40	40
E	13½	26½	40	—	40
F	1½	3½	5	—	5
A + B + C + D + E + F					100

The points of each parameter were added up by

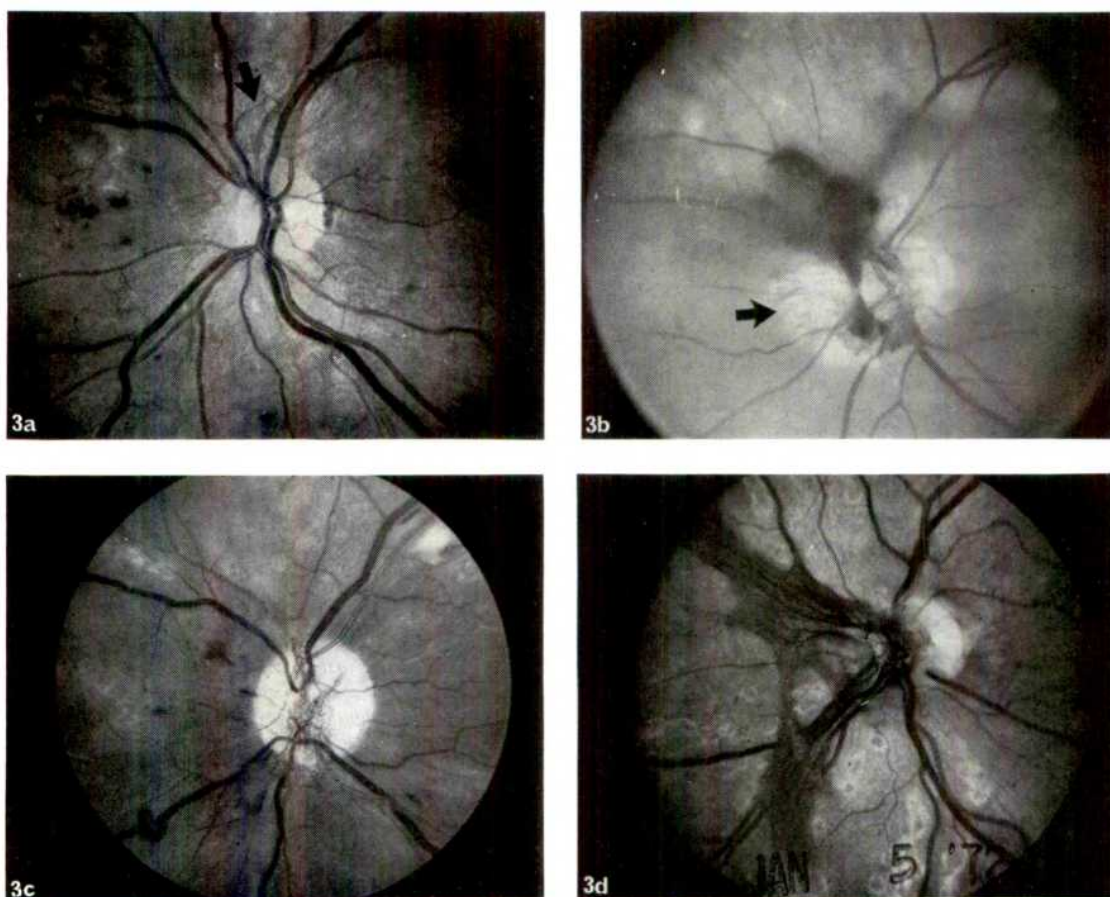
the clinician to a point score for NVD overall grading:

Table 2 Overall grading score of NVD

NVD overall grade	No. of points
1	1–30
2	31–60
3	61–90
4	91–100

The higher the number of points the more advanced is the disc neovascularisation.

According to this scheme four standard photographs (Figs. 5a–d) were established to facilitate NVD grading either by the point system or by comparing any disc photograph to the overall grade standard photograph it most closely resembles.



Figs. 3a-d The average density of disc neovascularisation is graded in 4 stages. Examples of each stage are demonstrated: 3a. Density of vessels stage I. 3b. Density of vessels stage II. 3c. Density of vessels stage III. 3d. Density of vessels stage IV.

Grading classification for the fibrous proliferation at the disc (FPD) was separately determined, and was based on 3 parameters:

A. The area of proliferation, with I-IV stages, as described for NVD area of proliferation.

B. Plane of proliferation, with I-III stages, as described for NVD plane of proliferation.

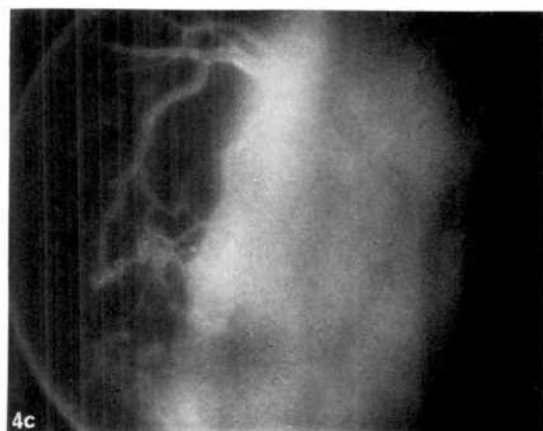
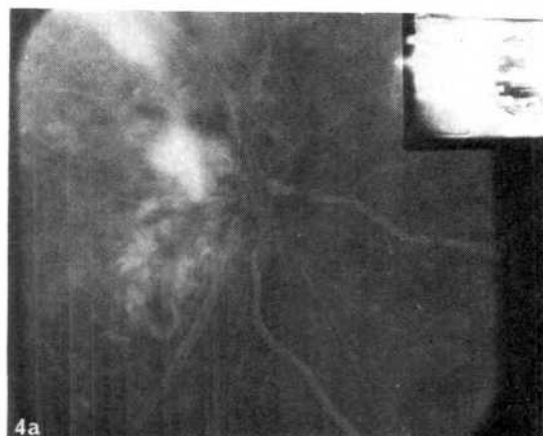
C. The density of the fibrous tissue (stages I-III), determined according to 6a, 6b, and 6d standard photographs. Here again, according to our observations on the natural history of FPD since 1960, each parameter received a relative score: parameter A received a score of 40 points toward 100, and parameters B and C received 30 points each. Each stage within each parameter received the points as follows:

Total no. of points for parameter
No. of stages composing the parameter

and the points were added to each other when moving up to the next stages of each parameter:

Table 3 Point system of stages and parameters of FPD

Parameter	No. of points of stage in parameter				No. of maximal possible points of parameter
	I	II	III	IV	
A	10	20	30	40	40
B	10	20	30	—	30
C	10	20	30	—	30
A + B + C					100



Figs. 4a–c Fluorescein leakage is graded from stage I, indicating a mild dye leakage, up to stage III, with maximum dye leakage evaluated in the films at approximately 1–2 minutes following the appearance of the dye in the retinal circulation: 4a. Stage I fluorescein leakage from the disc and from vessels inferior to disc showing mild amount of leaking dye. 4b. Stage II fluorescein leakage showing moderate amount of dye in the vitreous. 4c. Stage III fluorescein leakage showing heavy dye leakage into the vitreal space.

The points of each parameter were added up by the clinician to a point score for FPD overall grading:

Table 4 Overall grading score of FPD

FPD overall grade	No. of points
1	1–30
2	31–60
3	61–90
4	91–100

The higher the number of points, the more advanced is the disc fibrous proliferation.

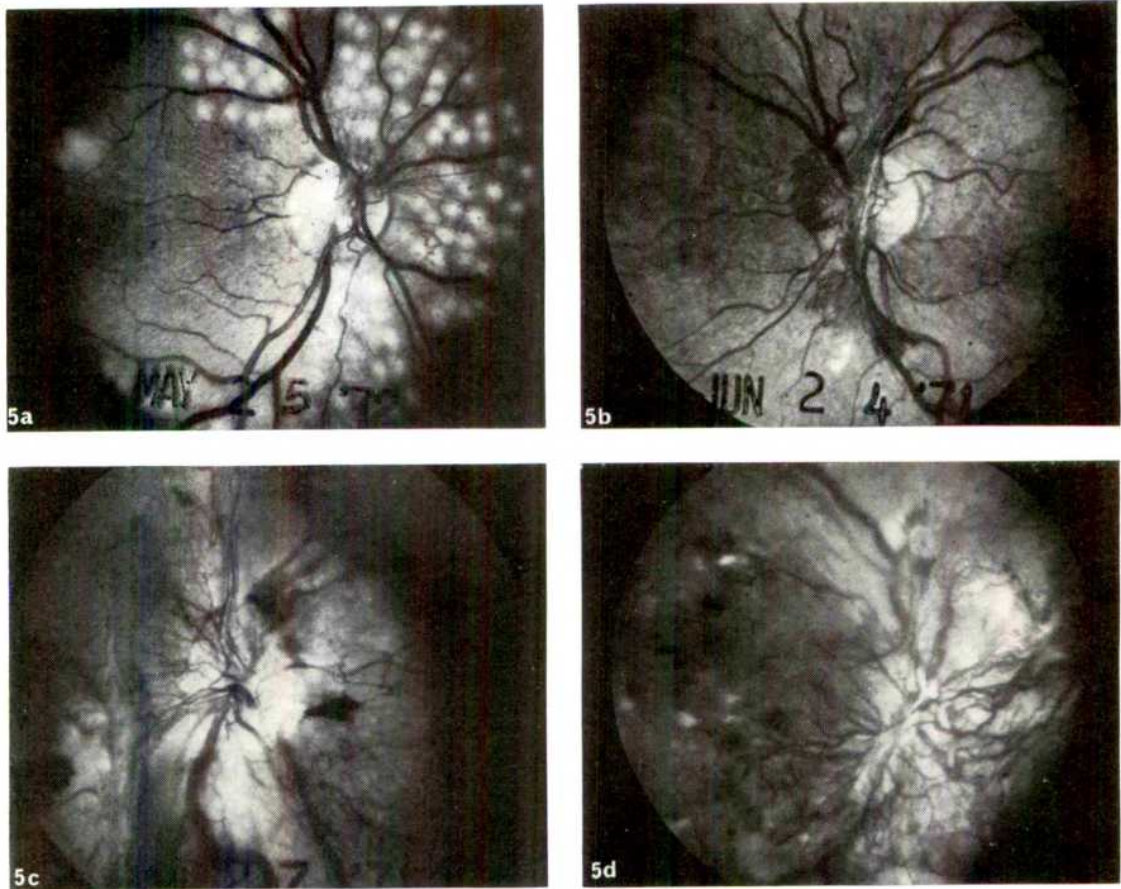
According to this, the following 4 standard photographs for an overall FPD grading were established, so that any examined disc fibrous proliferation may be graded either by the point

system or by comparing it to the overall grade standard photograph it most closely resembles (Fig. 6).

Discussion

Patients with neovascularisation emanating from the disc have a poor visual prognosis, and there is a high incidence of vitreous haemorrhage as well as fibrous proliferation and traction retinal detachment.

Any grading system for proliferation at the optic disc is arbitrary and based upon various considerations embedded in the author's clinical judgment as being relatively more significant. Most morphological descriptions of optic nerve head proliferation have been based on the general appearance of the disc, with the observer noting whether it was 'worse' or 'better' with time. A more systematic classification was laid by Kohner *et al.*,³ and it incorporated morphological as well as some quantitative para-

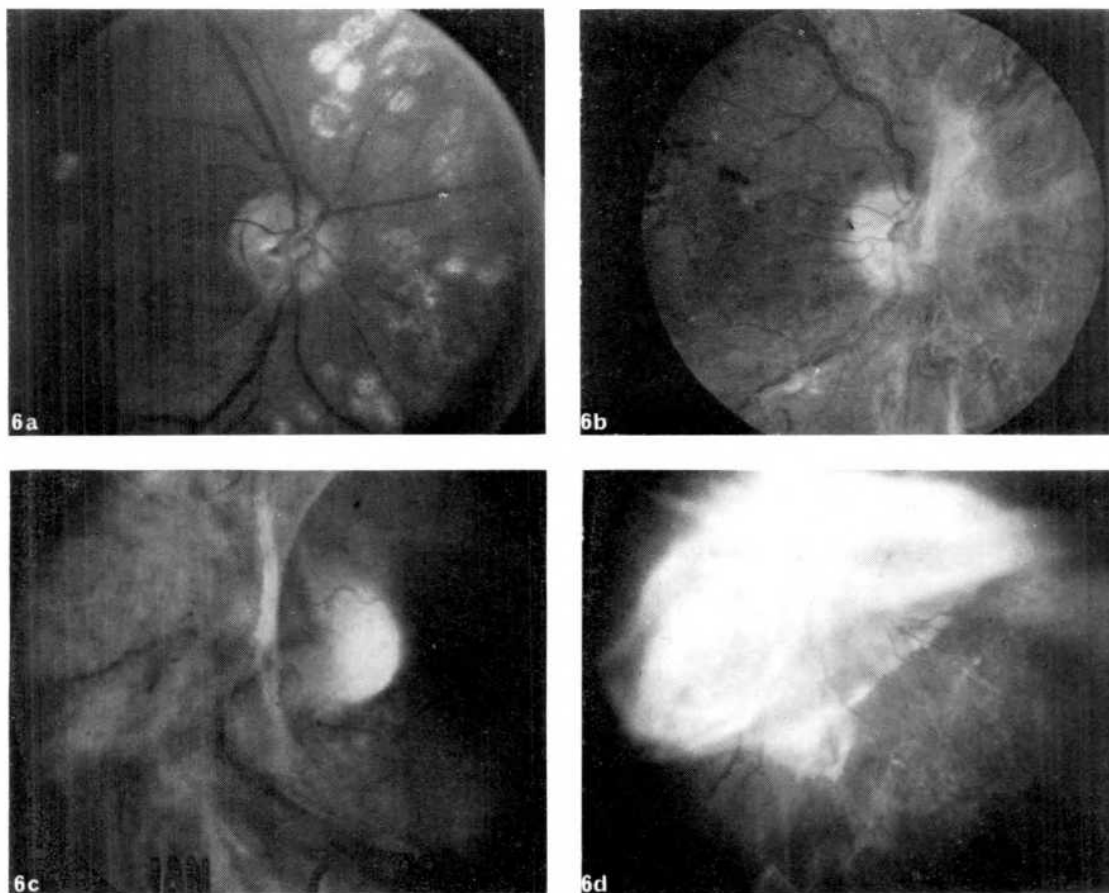


Figs. 5a–d Overall grading of disc neovascularisation: 5a. Grade 1 neovascularisation of the disc. 5b. Grade 2 neovascularisation of the disc. 5c. Grade 3 neovascularisation of the disc. 5d. Grade 4 neovascularisation of the disc.

meters. It has later been used by the British Multicentre Photocoagulation Trial Group.⁸ However, this system also had limitations, some of them expressed by the authors themselves: (1) Perceptible alterations in neovascularisation occur, without change in grade. (2) Density of new vessels is not graded. (3) A distinction between NVD and FPD was not used in that classification. Instead, when fibrous proliferation occurred, the NVD grading by that system was 'frozen'; NVD grading remained, therefore, almost unchanged, and the significance of moving from primarily neovascular proliferation to primarily fibrous proliferation could not be assessed. (4) The total area of NVD and FPD and the plane of proliferation could not be incorporated in the grading system, since stereophotography was originally not used. (5) Calibre of the new blood vessels was not graded.

L'Esperance's classification,⁴ although detailed in some morphological aspects, did not establish a taxonomy of grading and of evaluating progression or regression of either form of disc proliferation. The same is true of Hercules *et al.*'s classification,⁹ which is actually a modification of L'Esperance's classification. The Diabetic Retinopathy Study Research Group classification^{6,7} did not go into all details of NVD and FPD components.

The present study attempts to overcome these disadvantages. It is based on detailed parameters according to the experience accumulated out of approximately 600 patients with NVD and FPD, who have been observed since a natural history study was started in 1960. This classification also can discriminate between the evolution of NVD and FPD. New vessels are more apt to bleed, while fibrous tissue is more apt to cause gliosis of the



Figs. 6a–d Gradation of the amount of fibrous proliferation present at the disc: 6a. Grade 1 fibrous proliferation at the disc (also stands for density stage I of FDP). 6b. Grade 2 fibrous proliferation at the disc (also stands for density stage II of FDP). 6c. Grade 3 fibrous proliferation at the disc. 6d. Grade 4 fibrous proliferation at the disc (also stands for density stage III of FDP).

retina and traction retinal detachment. We often see that disc new vessels are replaced by fibrotic tissue, and the present taxonomy can follow the reciprocity between these 2 forms of disc proliferation.

By this taxonomy the variations in a particular disc can be followed for a time period without using general terms such as 'progression' or 'improvement', by recording the scores for the examined parameters. This taxonomy may permit a better understanding of follow-up of the natural history and results of treatment of disc proliferation in terms that can be used at different clinical centres by different examiners, and may serve until another classification is introduced according to future new knowledge.

Visual acuity was not incorporated in establishing this grading system. The visual acuity is undoubtedly the criterion by which the patient judges the changes of this disease and response to treatment. Nevertheless, there are so many other factors involved in determining visual acuity, such as macular oedema and degree of vitreous haemorrhage—and quite often vision at a certain time can be good in the presence of severe disc pathology and vice versa—that using visual acuity in the grading system would create an additional unnecessary bias in interpreting the status of the optic nerve head.

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Optic disc neovascularisation in diabetic retinopathy: II. Natural history and results of photocoagulation treatment

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SUMMARY A follow-up study on 67 diabetic patients with new proliferation on the nerve head (neovascularisation of the disc and fibrous proliferation of the disc) was carried out for 4 years. The patients were randomly assigned for treatment with argon laser and xenon photocoagulation in only one eye, with the other eye serving as a control. The disc condition was periodically evaluated for NVD, FPD, and for the relations between them according to a grading taxonomy which was previously established. It was found that there were significant differences in NVD and FPD evolution between treated and untreated eyes. The various parameters concerned with these differences were observed, analysed, and correlated.

Retinal neovascularisation in diabetic retinopathy occurs most commonly on the optic disc. It is the most serious complication of diabetic retinopathy as it frequently leads to vitreous haemorrhage and traction retinal detachment.^{1,2} The disc has a unique peripapillary capillary plexus.³ The absence of an internal limiting membrane over the disc⁴ may be responsible for the predilection to develop neovascularisation in that area.

Deckert *et al.*⁵ pointed out the poor prognosis of neovascularisation at the disc (NVD) in juveniles. 50% of patients who have NVD become legally blind within 2 to 3 years. Beetham *et al.*⁶ showed that 85% of untreated patients with proliferative diabetic retinopathy (PDR) and vitreous haemorrhage had this haemorrhage from NVD. Patz and Berkow⁷⁻⁹ also pointed out the bad prognosis of eyes with NVD and the fact that 50% of all patients with disc neovascularisation were legally blind 2 years after the diagnosis of NVD. Davis¹⁰ traced the fate of NVD, which first increases in size and amount, and then regresses, to be replaced by fibrous proliferation at the disc (FPD), which causes retinal traction. Davis¹¹ also stressed the role of posterior vitreous detachment in the pathogenesis of vitreous haemorrhage and retinal detachment in

NVD and FPD. These studies elicited clearly that disc new proliferation in proliferative diabetic retinopathy (PDR) is a major contributor to diabetic blindness.

Various modes of photocoagulation treatment, such as focal treatment in NVD, panretinal photocoagulation (PRP), and PRP combined with focal treatment in NVD, have been employed during the last 2 decades on eyes with NVD, with various sources of light energy (xenon arc, ruby laser, argon laser, and krypton laser). Various studies on results of treatment reported various conclusions. Aiello *et al.*^{12,13} and Beetham *et al.*⁶ reported favourable results of NVD regression in patients treated with ruby laser PRP, particularly when the treatment was performed early. Wessing and Meyer-Schwickerath¹⁴ reported only 20% regression of NVD in patients treated with xenon retinal photocoagulation, while Krill *et al.*¹⁵ reported much better results with the same modality, if treatment were extensive. Okun^{16,17} and Taylor and Dobree¹ also reported considerable NVD regression after extensive xenon PRP. Other reports claimed beneficial effects of argon laser photocoagulation in eliminating NVD, either by PRP alone¹⁸⁻²⁰ or by PRP and additional focal treatment, if necessary, at various times after PRP has been completed.^{2,9,21-23} L'Esperance^{24,25} stressed the good results of focal treatment on NVD. Arribas *et al.*²⁶ claimed to try all photocoagulation sources and techniques, and concluded that xenon arc PRP was most effective

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if applied early. They stated that good results cannot be obtained by xenon arc or argon laser when NVD was extensive and highly elevated into the vitreous.

Patz⁸ called for reports from controlled studies. These were first obtained from the British Multicentric Photocoagulation Trial,²⁷ which reported much regression of NVD in xenon-treated eyes; from the Diabetic Retinopathy Study Research Group,^{28, 29} which showed that eyes with NVD that were treated either with xenon arc or argon laser, especially early in the disease, had a considerable reduction of NVD; and from Hercules *et al.*,³⁰ who showed that in eyes treated by argon PRP alone there was a much higher reduction of NVD during the 3 years of follow-up than in untreated eyes with NVD, particularly if treated early in the disease.

In a previous study³¹ a taxonomy based on detailed parameters of disc new proliferation was laid out so that NVD and FPD could be evaluated separately. The present study involves a 4-year follow-up of treated and untreated eyes with disc new proliferation that examines the fate of this proliferation and the relation between NVD and FPD.

Material and methods

During 1973–4, before any results of controlled randomised therapeutic studies for NVD were available, patients seen in our clinic were randomly assigned for photocoagulation treatment. These patients had NVD of various grades, according to a grading system described by Yassur *et al.*,³¹ and only one eye was randomly assigned for treatment. None of the patients had pituitary ablation or previous photocoagulation treatment. Initially we reviewed the records of 83 consecutive patients assigned for a 4-year follow-up, but 16 patients dropped out at various stages because of death, inadequate follow-up, or because the 'control' eye was also treated. Therefore 67 patients, 35 of whom were men and 32 women, aged 16–72 years, with diabetes duration of 1–40 years (mean 18.4 years) were followed up for 4 years. Forty-five patients had argon laser photocoagulation treatment, and 22 patients had xenon arc photocoagulation treatment. The treatment consisted of PRP, according to the treatment protocol of the *Manual of Operation* of the Diabetic Retinopathy Study.³² All the eyes had adequate treatment from the point of view of the pattern and number, size, and intensity of the photocoagulation burns. Only 2 of the argon laser-treated patients had additional focal treatment to NVD within 6 months after completing the PRP.

The disc new proliferation, NVD and FPD, of the treated and untreated eyes was evaluated and

graded at the beginning of the study and then periodically every 6 weeks to 1 year up to 4 years. The evaluation of NVD and FPD was done according to the 6 parameters described in the grading system:³¹ number of involved disc quadrants, calibre of new vessels, density of NVD or FPD, total area of NVD or FPD proliferation, plane of NVD or FPD proliferation, and fluorescein leakage from NVD. The overall grading for each disc was assessed on the follow-up examinations by using stereophotographs and fluorescein angiography.

Results

There were marked and significant differences in most of the recorded parameters for NVD and FPD in treated and untreated eyes.

Fig. 1 demonstrates the deep gap between treated and untreated eyes concerning the number of quadrants involved in NVD.

Fig. 2 demonstrates some gap between treated and untreated eyes concerning calibre of vessels in NVD frond; however, all 3 curves have a mild upward inclination, which can be attributed to the 'maturing' process of blood vessels which remained in fronds.

Fig. 3 demonstrates the gap in density in NVD

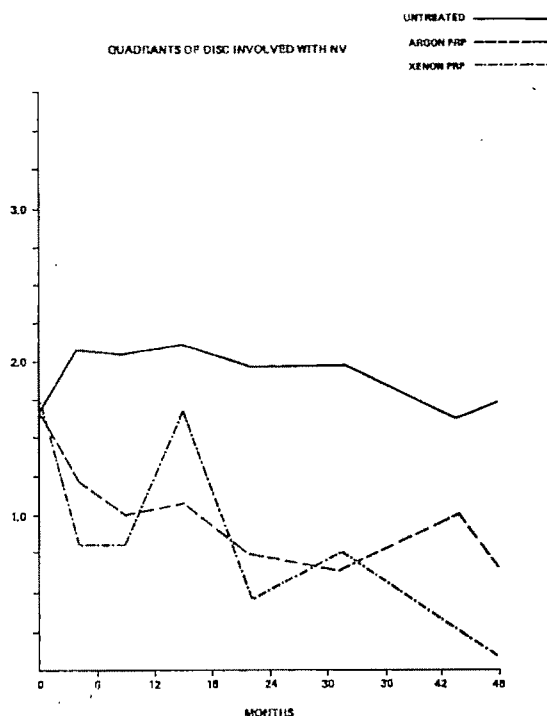


Fig. 1 Number of quadrants involved with NVD.

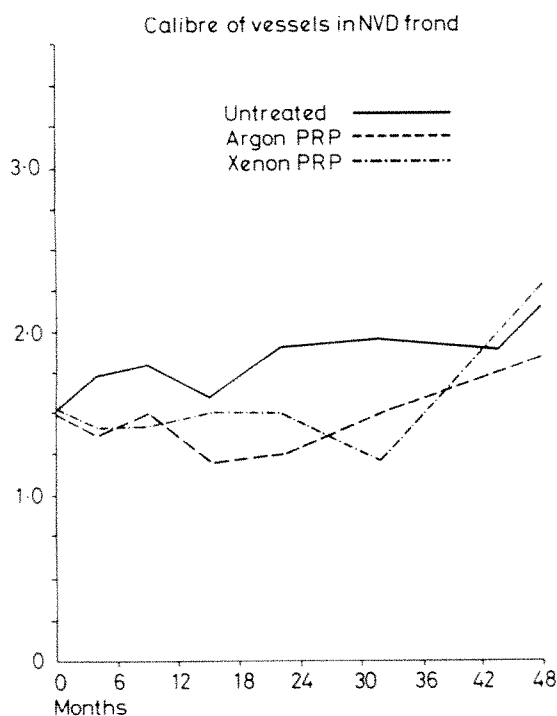


Fig. 2 Calibre of vessels in NVD frond.

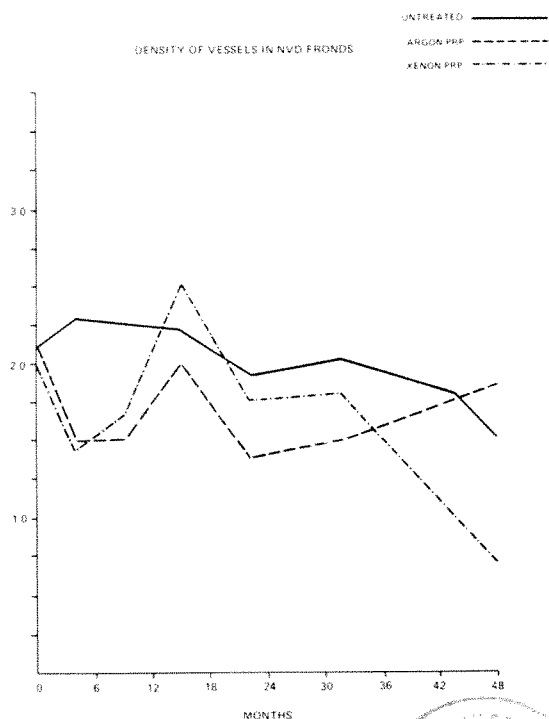


Fig. 3 Density of vessels in NVD frond.

fronds. The initial deep gap between the treated and untreated eyes is due to the good response to treatment, with partial regression of vessels in existing fronds.

Fig. 4 demonstrates the gap induced by treatment in total area of proliferation of NVD between treated and untreated eyes. This gap is due to reduction in NVD in treated eyes. The 'ups and downs' in the curves can be attributed to the dynamic transformation of existing NVD to FPD during various phases of the long follow-up period.

Fig. 5 demonstrates the plane of proliferation of

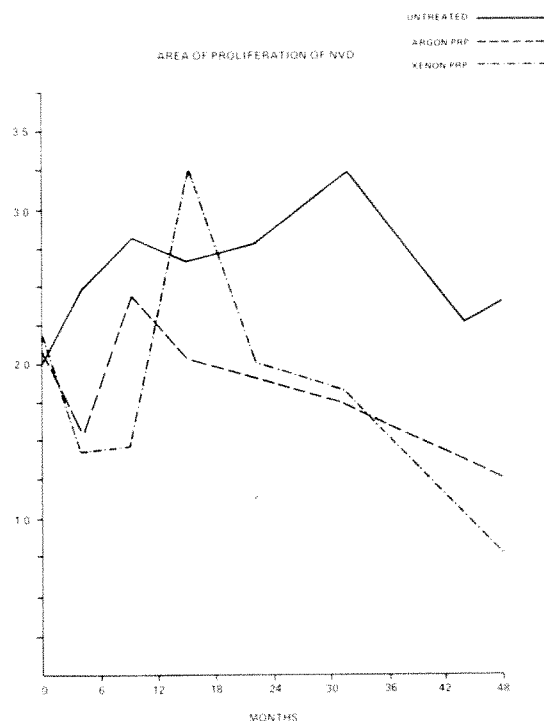


Fig. 4 Total area of proliferation of NVD, measured in DD.

NVD in treated and untreated group. It is true that the vitreous continued to detach further from the retina in the untreated eyes, as a signal of increased disc new proliferation, as demonstrated earlier by Davis.¹¹ However, xenon arc treated eyes also showed such a rising slope, which may be explained by more heating of the vitreous with xenon therapy compared to argon therapy.

Tables 1-7 demonstrate additional aspects of the follow-up investigation. The numbers in italics represent those eyes in which no change of grade occurred. The numbers to the left of them represent eyes with a decrease in grade, or less involvement.

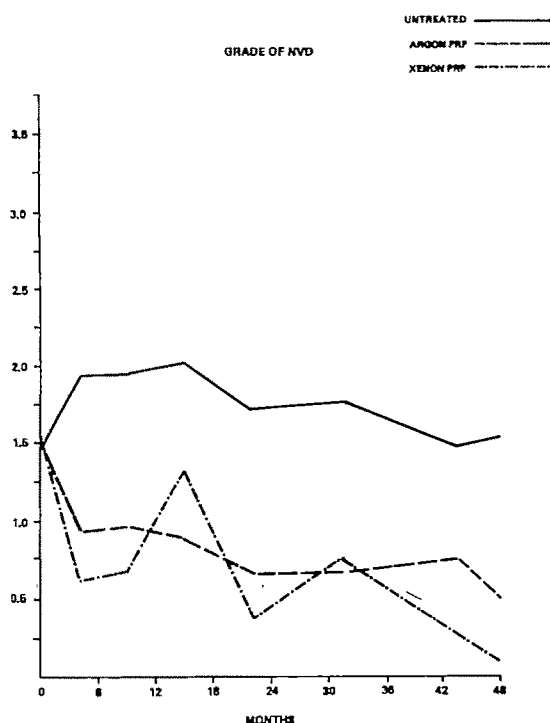


Fig. 6 Overall grade of NVD.

proliferation; however, this disappearance and replacement in the treated eyes occurs at a much lower level of grading.

Table 4, which summarises the fate of NVD during the follow-up period, demonstrates the significant difference between treated eyes, of which 88% either decreased or remained at the same NVD grade, and untreated eyes, of which only 46% either decreased or remained at the same NVD grade.

Table 5 shows the percentage of eyes which had no NVD at the end of the follow-up period from those who had NVD at the beginning of the study in each NVD grade group. It is demonstrated that, in the argon- and xenon-treated eyes, between 50% and 75% of eyes in NVD grade 1-3 groups eventually had no NVD, while in the untreated eyes only 6-14% eventually had no NVD. The number of eyes in this study in group 4 NVD grade was too small to draw conclusions; however, the bad prognosis of such eyes has already been established.

Table 6 demonstrates the high significance of difference concerning the increase in NVD grade between treated and untreated eyes. There is no difference in the increase of NVD grade between argon- and xenon-treated eyes: both did equally well compared to untreated eyes, which showed a significant increase in NVD overall grade.

Table 7 demonstrates that the decrease in NVD grade in both argon- and xenon-treated eyes was significantly higher than in the untreated eyes. Here too there is no significant difference between argon- and xenon-treated eyes: in both treated groups the NVD grade decreased considerably.

Table 8, which represents the FPD grade in argon-treated eyes, demonstrates that FPD grade increased in 31%, remained the same in 60%, and decreased in 9%. This reflects the fact that in a good majority of the treated patients in which regression of NVD occurred the regression happened with the NVD not being replaced by FPD.

Table 4 The fate of NVD during the 4 years of follow-up—summary table (numbers of patients in parentheses)

NVD grade	Argon treated eyes	Xenon treated eyes	All treated eyes	Untreated eyes
Decrease	71% (32)	64% (14)	69% (46)	22% (15)
Same	18% (8)	23% (5)	19% (13)	24% (16)
Increase	11% (5)	13% (3)	12% (8)	54% (36)
Total	100% (45)	100% (22)	100% (67)	100% (67)

Table 5 Percentage of eyes graded 0 for NVD on last visit by initial grade

	Initial grade			
	1	2	3	4
Argon treated	72%	45%	36%	0%
Xenon treated	55%	57%	75%	0%
Untreated eye	14%	6%	0%	0%

Table 6 Significance of increase in NVD grade during the 4-year follow-up period

Group	% of Eyes with increased NVD grade	Z	P value
Argon treated eyes	11%	4.08	<0.001
Untreated eyes	54%		
Xenon treated eyes	13%	2.90	0.004
Untreated eyes	54%		
All treated eyes	12%	4.51	<0.001
Untreated eyes	54%		
Argon treated eyes	11%	-0.30	0.76
Xenon treated eyes	13%		

Table 7 Significance of decrease in NVD grade during the 4-year follow-up period

Group	% of Eyes with decreased NVD grade	Z	P value
Argon treated eyes	71%	-4.64	<0.001
Untreated eyes	29%		
Xenon treated eyes	64%	-2.93	<0.004
Untreated eyes	29%		
All treated eyes	69%	-4.95	<0.001
Untreated eyes	22%		
Argon treated eyes	71%	0.62	0.52
Xenon treated eyes	64%		

Table 8 Grade of FPD before treatment versus grade 4 years after argon laser treatment

		<i>Last visit</i>						
<i>Grade</i>		<i>0</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>Total number of eyes</i>	
<i>Initial visit</i>	<i>0</i>	22	5	3	1	0	31	
	<i>1</i>	2	5	2	1	1	11	
	<i>2</i>	0	1	0	1	0	2	
	<i>3</i>	0	0	1	0	0	1	
	<i>4</i>	0	0	0	0	0	0	
Total number of eyes		24	11	6	3	1	45	

Table 9 Grade of FPD before treatment versus grade 4 years after xenon treatment

Grade	0	1	2	3	4	Total number of eyes
0	6	5	2	2	2	17
1	0	0	3	0	0	3
2	0	0	0	0	2	2
3	0	0	0	0	0	0
4	0	0	0	0	0	0
Total number of eyes	6	5	5	2	4	22

Table 9, which represents FPD grade in xenon-treated patients, demonstrates that more than two-thirds of the eyes (73%) showed increase in FPD grade, and less than one-third (27%) showed the same grade of FPD. None of the eyes had a decrease in FPD grade. This happened because in a good majority of eyes in this group the NVD which

regressed was replaced by FPD, and only in one-third the NVD which regressed was not replaced by fibrous tissue.

Table 10, which represents the FPD grade in untreated eyes, demonstrates that in more than half of the eyes (57%) there was a considerable increase in FPD grade, while in less than half of the eyes (43%) the FPD grade remained the same. This reflects the fact that as NVD continued to grow and was later replaced by FPD, the amount of fibrosis on the disc increased too.

Fig. 7, which represents the plane of proliferation

Table 10 Grade of FPD at first visit versus grade 4 years later in untreated eyes

		Last visit					Total
		Grade	0	1	2	3	4
Initial visit	0	23	8	7	3	8	49
	1	0	3	3	3	1	10
	2	0	0	3	2	3	8
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
Total		23	11	13	8	12	67

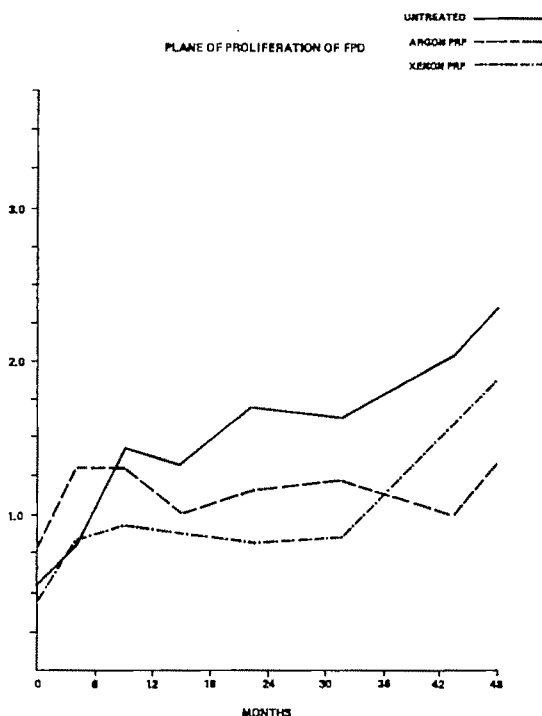


Fig. 7 Plane of proliferation of FPD.

of FPD, demonstrates that there is a gap between the curves of treated and untreated eyes, although all 3 curves show an upward inclination, which is due to the continuous detachment of the posterior vitreous face away from the surface of the retina. Again, as in the plane of proliferation for NVD, the rate of this detachment is more accelerated in untreated eyes, and somehow more accelerated eventually in xenon-treated than in argon-treated eyes, perhaps due to more contraction of vitreous in xenon-treated eyes.

Fig. 8, which represents the overall grade of FPD, demonstrates the deep gap between treated and untreated eyes. This is attributed to the fact that, as more NVD grows, it is later replaced by more FPD; and the earlier the growth of NVD is prevented the less likely that FPD will emanate from the disc later. The curve of argon-treated eyes suggests that, immediately after the first response to PRP treatment, some of the regressing NVD is replaced by FPD, but later there is some regression of some of the fibrotic tissue and also dynamic transformation of NVD to FPD on a much lower level than for untreated eyes. In the xenon-treated eyes the process was similar to that in the argon-treated eyes, except that the net effect was greater develop-

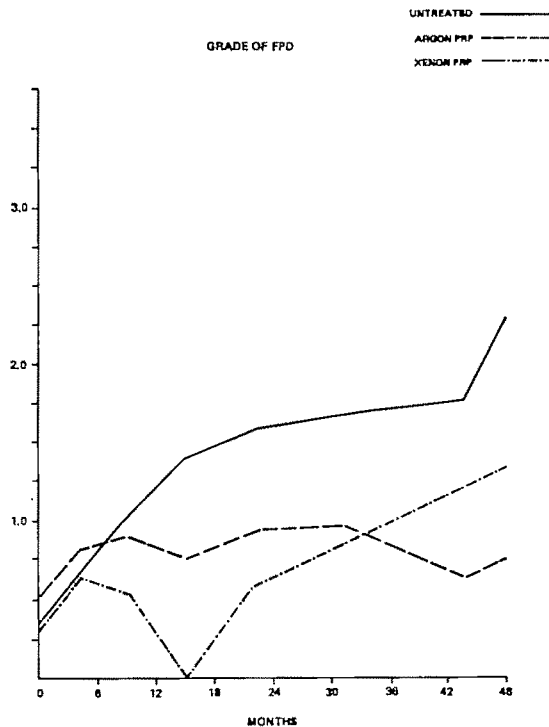


Fig. 8 Overall grade of FPD.

Table 11 The fate of FPD during the 4 years of follow-up—summary table (number of patients in parentheses)

FPD grade	Argon treated eyes	Xenon treated eyes	All treated eyes	Untreated eyes
Decrease	9% (4)	0% (0)	9% (6)	0% (0)
Same	60% (27)	27% (6)	40% (32)	43% (29)
Increase	31% (14)	73% (16)	42% (29)	57% (38)
Total	100% (45)	100% (22)	100% (67)	100% (67)

Table 12 Percentage of eyes graded 0 for FPD on last visit by initial grade

Initial grade	0	1	2	3	4
Argon treated	71%	18%	0%	0%	0%
Xenon treated	46%	0%	0%	0%	0%
Untreated eyes	26%	0%	0%	0%	0%

ment of FPD compared to the argon-treated eyes.

Table 11 summarises the fate of FPD in the treated and untreated eyes. It is demonstrated that about half of both treated and untreated eyes had an increase of FPD grade, about half had the same FPD grade, and only one-tenth of treated eyes had a decrease in FPD grade. This demonstrates again that the basic process of NVD disappearance is either a mere regression or regression and replacement by FPD; the less NVD which exists and the earlier NVD disappears, the less FPD occurs later. Most of the FPD in treated eyes occurred on a lower grade level than in untreated eyes.

Table 12 represents the percentage of eyes which had no FPD at the end of the follow-up period from those who had no FPD at the beginning of the study in each FPD grade group. In the argon-treated eyes as high as 71% which were graded 0 for FPD remained 0, and 18% of eyes graded 1 for FPD remained 1. All the rest had some FPD to some degree. In xenon-treated eyes 46% previously graded as 0 still remained 0 for FPD, while all the others had some FPD grading. In the untreated group only 26% of eyes which had 0 FPD grade remained so, while the rest developed FPD. This again demonstrates the fact that evolution of NVD to FPD calls for eliminating NVD sooner in order to prevent FPD complications.

Table 13, which represents the significance of increase in FPD grade, demonstrates that in our

Table 13 Significance of increase in FPD grade during the 4-year follow-up period

Group	% of Eyes with increased FPD grade	Z	P value
Argon treated eyes	31%	2.81	0.005
Untreated eyes	57%		
Xenon treated eyes	73%	-1.19	0.23
Untreated eyes	57%		
All treated eyes	42%	1.81	0.7
Untreated eyes	57%		
Argon treated eyes	31%	-2.87	0.004
Xenon treated eyes	73%		

Table 14 Significance of decrease of FPD grade during the 4-year follow-up period

Group	% of Eyes with decreased FPD grade	Z	P value
Argon treated eyes	9%	-3.01	0.002
Untreated eyes	0%		
Xenon treated eyes	0%	0	0
Untreated eyes	0%		
All treated eyes	7%	-2.56	0.01
Untreated eyes	0%		
Argon treated eyes	9%	1.37	0.7
Xenon treated eyes	0%		

data the differences were significant concerning only argon-treated eyes versus untreated eyes, and argon-treated eyes versus xenon-treated eyes. However, it was our clinical impression that the difference was true also for xenon-treated eyes, and that FPD grade increased more in untreated eyes than in these eyes too.

Table 14, which represents the significance of decrease of FPD grade, demonstrates clearly that the difference in reduction of FPD grade, if occurring, between all treated eyes and untreated eyes was very significant. It was also our clinical observation that only eyes which were treated early enough and in which the FPD grade was mild showed the capability for this mild fibrotic tissue to disappear completely or considerably.

Fig. 9 demonstrates graphically the process of disappearance of NVD and its replacement by FPD. In all 3 curves there is a decline which is attributed to that mutual relationship between NVD and FPD. The less time NVD exists and the less NVD to exist, the sharper is the initial decline; and later the gap between treated and untreated eyes is generally maintained, with some variations during the follow-up period. The downward inclination of

the curves indicates that when the NVD grade decreases the FPD grade increases.

Fig. 10 demonstrates the changes in visual acuity in treated and untreated eyes. There is a permanent increase of the curve of untreated eyes, representing the fact that the visual acuity in the untreated eyes steadily decreased during the 4-year follow-up period. The curve of argon-treated eyes did not change much. The curve of the xenon-treated eyes showed very wide variations during the follow-up period.

Discussion

The taxonomy for grading system which was used in this study enabled us to provide a careful evaluation of the disc status in any of the 4-year follow-up visits, and to consider separately vascular and fibrous proliferation at the disc and to correlate them with each other.

It was shown that the evolution of NVD and FPD in treated eyes was significantly different from that in untreated eyes. All the parameters involved in overall grading of NVD and FPD were influenced by the argon and xenon treatment in such a way that disc proliferation was reduced.

The treatment seems to change the natural history

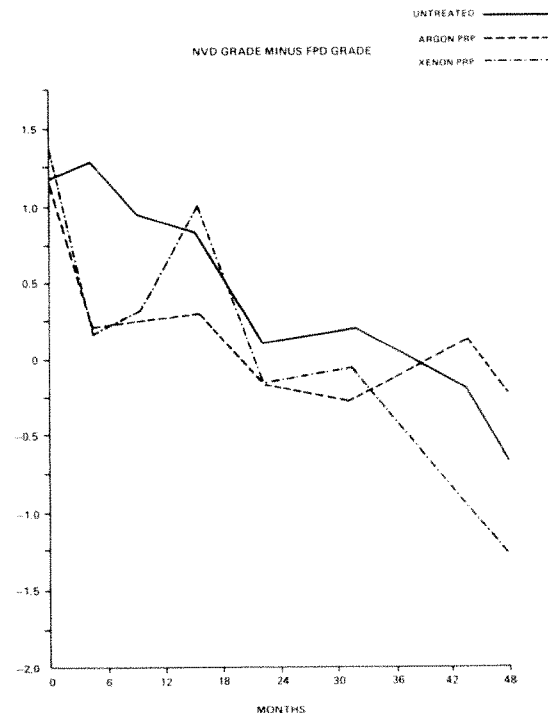


Fig. 9 NVD grade minus FPD grade.

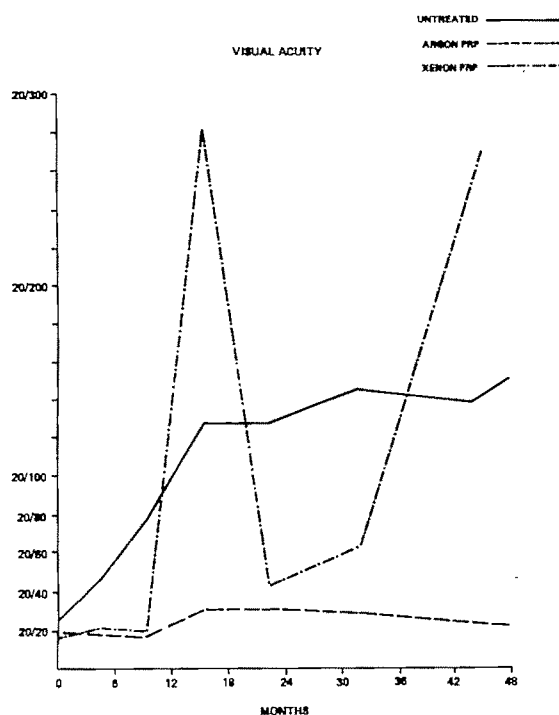


Fig. 10 Visual acuity of treated and untreated eyes.

of disc new proliferation either by preventing it from occurring or by shortening the duration of the disc pathology, hence reducing its adverse effect sequela.

A few observations and conclusions can be drawn from the results of the study:

Treated eyes, either argon- or xenon-treated, had less NVD at the end of the 4 years of follow-up than they had before they were treated. Untreated eyes had more NVD at the end of the follow-up period than they had at the beginning of the study.

Treated eyes, either with argon or with xenon, had less NVD and FPD at the end of the 4-year follow-up than had untreated eyes. The decrease in NVD grade in the present study in the treated eyes is 2.5 times that in the untreated eyes, and the increase in NVD grade in the untreated eyes is 3 times the increase in the treated eyes. This corresponds with the British Multicentric Photocoagulation Trial²⁷ and with the Diabetic Retinopathy Study Group's observations,^{28, 29} which showed that treatment of eyes with NVD either with xenon or with argon was beneficial to all kinds of NVD, with or without vitreous haemorrhage, and that the rate of disappearance of NVD in the treated eyes was 4 times that in untreated eyes, and that NVD existed 2-fold in untreated eyes compared to treated eyes.

The involution of active neovascularisation and reduction of vitreous haemorrhage noted in the previously listed studies²⁷⁻²⁹ and in our study in both argon laser and xenon photocoagulated eyes was most encouraging. However, we felt that a closer analysis of fibrous proliferation from the disc in these treated eyes had a major clinical significance. A common observation after involution of neovascularisation is the development of traction retinal detachment in the posterior pole, which may extend to the macula. NVD disappears on 2 lanes: it is either replaced by FPD or merely regresses without being replaced by FPD. The longer NVD exists, as in the untreated eyes, the more likely it is that it will disappear along the first lane, that is, by being replaced by FPD. The shorter time it exists and the lesser grade it is, the less fibrous proliferation will occur on the disc when it regresses. This was shown by the fact that FPD grade in untreated eyes increased considerably while FPD grade in treated eyes increased slightly or moderately. Our observation of much less fibrous proliferation after photocoagulation of early NVD suggests an additional benefit to the diabetic patient of prompt recognition and treatment of NVD. The significantly greater extent of FPD in xenon-treated eyes than argon laser-treated eyes which we have demonstrated (Table 13) represents an important detrimental effect of this modality, if longer follow-up shows a higher incidence of traction retinal detachment in this group. Further studies of FPD and its long-term consequences may help elucidate this issue.

There is no significant difference in the effect on disc NVD between argon- and xenon-treated eyes.

Correspondingly, treated eyes which show following treatment less NVD and FPD have better visual acuity than untreated eyes. As already pointed out,²¹ visual acuity measurements do not reflect the NVD and FPD status at each follow-up period. There is a tendency for untreated eyes to have over the long run a worse visual acuity; but it often happens during various follow-up visits that eyes with very advanced NVD still have good vision, while eyes with less advanced NVD have less good vision, due to vitreous haemorrhage or macular oedema. In this study these accidental variations are reflected by the xenon-treated eyes curve (Fig. 10), because these eyes had more vitreous haemorrhage from NVD and NVE than argon-treated eyes during the follow-up period.

If NVD exists, earlier treatment will probably induce regression of blood vessels better than later treatment or no treatment at all, and may also reduce future development of FPD. This conclusion is confirmed by the findings of the Diabetic Retino-

pathy Study Group^{28,29} and Hercules *et al.*,³⁰ who advocate early treatment.

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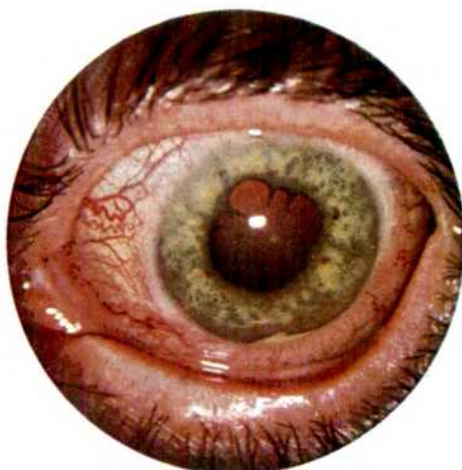
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Peripheral retinal ablation in the treatment of proliferative diabetic retinopathy during pregnancy

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SUMMARY The course of proliferative diabetic retinopathy involving the optic disc was followed, and the response to peripheral retinal photocoagulation monitored by argon laser in 11 patients during and after 13 pregnancies. Traditional obstetric practice assumes that pregnancy is a stimulus to irreversible progression of proliferative diabetic retinopathy, and that timely abortion and sterilisation are essential in order to achieve control of the neovascular process. Extensive photocoagulation will cause significant regression of neovascular complexes in 63% of cases, and it confers sufficient benefits to make ophthalmic indications for therapeutic abortion and sterilisation no longer tenable.

Taylor and Dobree¹ stated that between 68 and 73.25% of patients presenting with proliferative diabetic retinopathy have neovascularisation involving the optic disc. In a 3-year study Beetham *et al.*² showed that 85% (28 patients) of untreated eyes with vitreous haemorrhage bled from new vessels at the optic disc. This group of patients, exhibiting neovascularisation of the optic disc, inevitably have the poorest prognosis. Consequent on haemorrhage one-third of involved eyes are blind and one-third have permanent impairment of vision within 1 year.³ This is the most serious potential hazard for visual prognosis;⁴ 50% of these diabetic patients are blind within 2 to 3 years. If one eye becomes blind, Patz and Berkow⁵ have shown that the second (good) eye follows rapidly (50% within 1 year).

New vessels in proliferative diabetic retinopathy tend to progress during 9 months of activity in many cases, and it is therefore difficult to assess the effect of pregnancy on the course of this process. Reports on the subject come to no firm or convincing conclusions, but the risk to vision of rapidly advancing retinopathy during pregnancy has been stated to be high. Diabetic patients have frequently been advised against pregnancy if retinopathy has been present.⁶ From 200 pregnant diabetics attending the Joslin clinic with ocular symptoms Beetham⁷ found 12 patients (18 pregnancies) with proliferative retinopathy and observed progression of the neo-

vascular process in 4. Janert *et al.*⁸ observed progression of retinopathy in all 6 of their patients. White⁹ described 87 pregnant diabetics with proliferative retinopathy: 10 showed haemorrhagic activity prior to or during the first trimester; 11 of the 20 eyes progressed to blindness. She noted that eye lesions may improve after delivery, and that abortion is indicated (i) when retinopathy is deteriorating and (ii) when blindness might be expected if the pregnancy is continued. This tendency to regression of proliferative retinopathy after delivery has also been observed by Lawrence,¹⁰ Stephens *et al.*,¹¹ Janert *et al.*,⁸ and Laws *et al.*¹²

Driscoll and Gillespie¹³ considered advancing retinal neovascularisation, but not mere existence of retinopathy or blindness, an indication for termination of pregnancy. They also considered advanced retinopathy, and a high risk of ensuing blindness in the foreseeable future, constituted valid grounds for sterilisation.

Okun *et al.*¹⁴ noted that in 6 out of 10 diabetic patients proliferative retinopathy progressed rapidly during pregnancy. After termination the rate of growth of new vessels lessened, but they regressed in only 1 case. Burt and Weaver¹⁵ reported 2 cases of proliferative retinopathy in successfully pregnant women. One improved only after delivery, when pituitary ablation was undertaken, and the other improved during the course of pregnancy. They concluded that patients should be managed individually rather than routinely recommended for therapeutic abortion. Kohner *et al.*¹⁶ demonstrated that rapidly advancing proliferative retinopathy

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could be contained during pregnancy by photocoagulation and afterwards by pituitary ablation.

In view of the suggestions of other workers and before any of their results were available a trial was initiated in Manchester in 1973 to attempt elimination of optic-disc neovascularisation in the diabetic patient by peripheral retinal ablation.¹⁷ During the course of this study 5 pregnant women were admitted and every attempt was made to contain the proliferative process during their 6 pregnancies. Subsequently 6 more pregnant patients with optic disc neovascularisation were admitted to the group to give a total of 11 women and 13 pregnancies.

Patients and methods

Five pregnant women were entered into a randomised, controlled trial of 94 consecutive patients with a reasonably symmetrical proliferative diabetic retinopathy involving the optic disc. They had a visual acuity which did not differ by more than 2 lines on the Snellen chart and was at least 6/24 in the worse eye. Subsequently a further 6 women with optic disc neovascularisation were grouped with the women from the controlled trial. This latter group either were receiving argon laser photocoagulation when they discovered they were pregnant or commenced treatment soon after this event. No patient was excluded from the study for any of the reasons laid down in the study protocol.¹⁷

TECHNIQUE

All treated eyes were subjected to extensive peripheral retinal photocoagulation by means of a Coherent 800 gas-argon laser, incorporating a 3 mirror Goldmann lens in the delivery system¹⁸ when necessary. The procedure was well tolerated after instillation of local anaesthetic drops in all patients.

Photocoagulation burns were applied within the vascular arcades above and below the macula, but an approximately circular area of radius $2\frac{1}{2}$ disc diameters, with the fovea at its centre and including the papillomacular bundle, was left untouched. In the nasal fundus photocoagulation was extended centrally to the edge of the optic disc and involved any new vessels arising from this margin. In all meridians photocoagulation was extended anteriorly to the equator by means of the 3-mirror lens.

Individual burns with sufficient energy to accomplish minimal retinal blanching were applied so that the observer achieved a uniform response over the whole area being treated. Marker burns of 200 μ m diameter were applied to delineate the central area which was to be avoided. Inside the vascular arcades the 200 μ m spot diameter was

used. Outside the arcades and nasally, the 500 μ m spot diameter was used exclusively as far as the periphery. In the nasal sector burns were applied from the nasal edge of the optic disc to the equator in radial rows which followed the direction of the nerve fibres.

Energy levels between 0.2 and 0.6 watt were used, though most burns required 0.35 to 0.45 watt. Inferiorly higher energy levels were required than in any other area of the retina. Lower energies of 0.2 watt were almost invariably adequate within the macular vascular arcades of vessels, where the 200 μ m spot was used. In other areas utilising the 500 μ m spot levels up to 0.5 watt were usually required. To complete treatment over 2000 burns were applied to most patients (range 800 to 3000). The procedure usually required up to 6 sittings over a week.

Retreatment of areas which appeared unduly lightly treated and of any patches of untreated retina within the 'target' area of the ablation procedure was undertaken in patients in whom optic disc neovascularisation persisted.

DATA RECORDED

Patients entering the trial received a full ophthalmic assessment including refraction, tonometry, visual fields, fundus photography, and fluorescein angiography. Patients were not excluded from the study group on the basis of nephropathy or other serious extraocular diabetic problems. However, during and after treatment every attempt was made to achieve good diabetic control by careful medical assessment. The eye to be treated was chosen at random and the untreated eye recorded as a control.

Evaluation of treatment was based on four main criteria: (1) Visual acuity: best corrected visual acuities were obtained at each visit, on subjective testing, by a refractonist who was not aware of the previous visual acuity nor the treated eye. (2) Appearance of the optic discs 6 months after treatment and yearly from that point. Assessment was aided by colour photographs and fluorescein angiograms. (3) Vitreous haemorrhage and other complications including uveitis, glaucoma, and retinal detachment. (4) Blindness: eyes were accepted as blind as an end result of the proliferative process and/or vitreous haemorrhage if this involved a fall of visual acuity to less than 6/60 on the Snellen chart. This result had to be recorded on at least two consecutive visits.

Patients were reviewed at intervals of 2 weeks, 1 month, and 4 to 6 months after the completion of peripheral retinal ablation. Further assessment included visual fields, retinal colour photography, and fluorescein angiography.

Results

For the purposes of the study the 11 pregnant patients were compared with the nonpregnant women contained in the randomised, controlled trial of peripheral retinal ablation.¹⁷ Exclusions from the study were made if the patient conformed to one of the following criteria: (i) postmenopausal, at first attendance with proliferative retinal changes; (ii) pregnancy had occurred since proliferative retinal changes were first identified but prior to assessment in our clinic.

Finally the 2 groups of women were compared with all the men entered into the initial randomised, controlled study. The findings are shown in Table 1.

Table 1 Population studies of patients in comparative groups

	Women		Men
	Pregnant	Nonpregnant	
Age (mean) in years	26	36.5	42
Duration of diabetes (years)			
(i) mean	17.73	17.0	18.45
(ii) range	10→25	8→32	2→40

OPTIC DISC NEOVASCULARISATION

Regression of new vessels at the optic disc was assessed on the basis of status at initial examination and subsequent change recorded 6/12 after completion of photocoagulation,¹⁷ or, in the case of the pregnant women, 6/12 after the end of the gestational period (Figs. 1–6).

In the pooled female groups all patients experienced a measurable degree of vessel regression, while the male group had 7.4% of cases in which the neovascular situation either remained stable or deteriorated. A less than significant response was measured in 36.4% of pregnant women, 33% of nonpregnant, and 9.2% of men. A significant improvement in vessel status was recorded in 63.6% of pregnant women, 66% of nonpregnant, and 83% of men (Table 2a, b).

Table 2a Initial grading of retinopathy at optic disc (according to classification of Hercules et al.¹⁷)

	Total number of patients in grade		
	Pregnant	Nonpregnant	Males
Grade 1	3	12	21
2	6	5	29
3	2	4	4
Total	11	21	54

Table 2b Percentage regression of new vessels at optic disc (<50% is considered to be nonsignificant)

Vessel regression	Total number of patients		
	Pregnant	Nonpregnant	Males
100%	2	8	19
>50%	5	6	25
<50%	4	7	5
Same or advancing	0	0	4

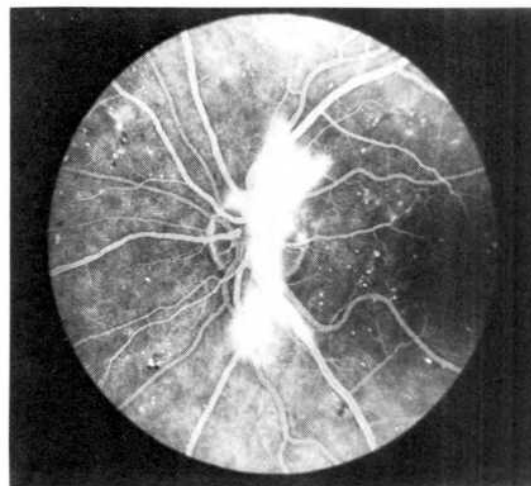


Fig. 1 Fluorescein angiogram showing early papillo-vitreal neovascularisation of the disc at the end of the first trimester of pregnancy.

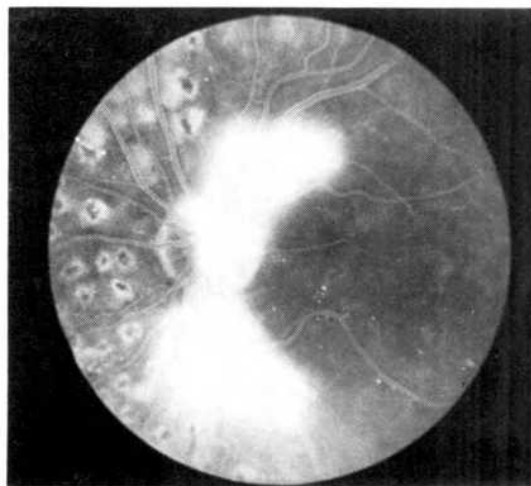


Fig. 2 Fluorescein angiogram of the fundus in Fig. 1 at 28 weeks. Peripheral retinal photocoagulation has been undertaken. Laser scars are either 1 or 12 weeks old. There has been an increase in new vessels along the temporal arcades.

VITREOUS HAEMORRHAGE

The mean time to vitreous haemorrhage, and the occurrence of this event, were recorded in both treated and control eyes. The results are shown in Table 3a, b.

In the randomised, controlled trial, the mean time to the onset of vitreous haemorrhage from the start of treatment was evaluated in treated and control eyes. The difference in mean time to vitreous haemorrhage, expressed in years, for all treated

groups and for the control groups was very highly significant (Mann-Whitney U test, $P < 0.0001$).

BLINDNESS

Table 4 outlines the number of eyes in each of the 3 groups which proceeded to blindness within the first 3 years after photocoagulation.

In the randomised, controlled trial the difference in proportions between treated and control eyes

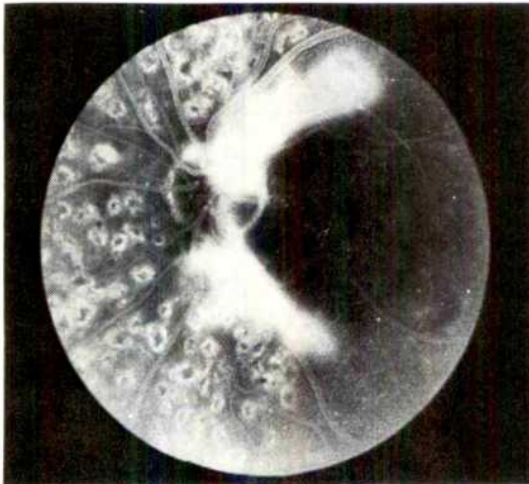


Fig. 3 Fluorescein angiogram shows the fundus of Fig. 1 6 months after the successful completion of pregnancy. There is no further advance of the 'arcuate' papillovitreal complex, and the vascular component is increasingly attenuated.

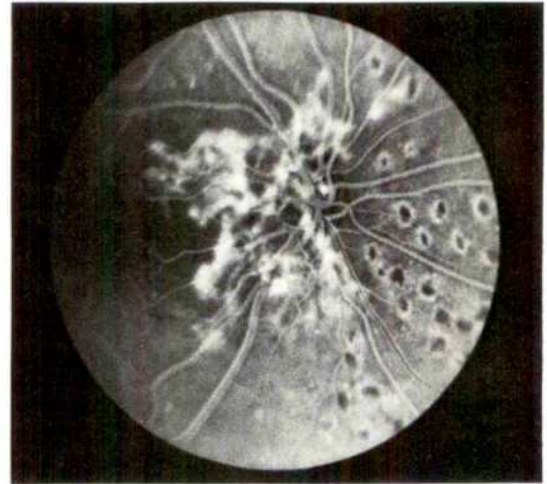


Fig. 4 Fluorescein angiogram showing extensive peripapillary neovascularisation with early glial tissue deposition after 12 weeks of pregnancy. Old argon laser burns are seen in the nasal fundus. This treatment was undertaken in the active phase of new vessel growth 3 weeks prior to pregnancy.

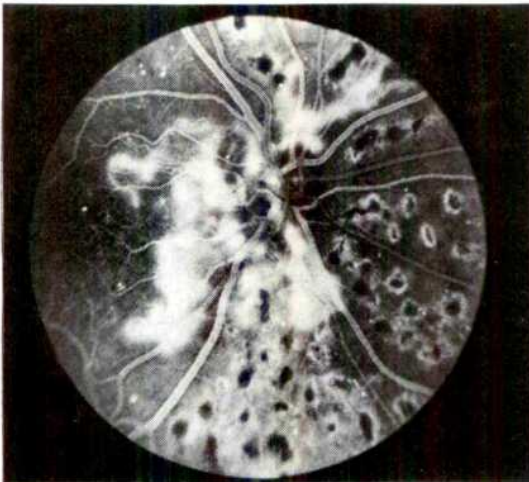


Fig. 5 Fluorescein angiogram showing the fundus of Fig. 4 with further argon laser applications in lightly treated and untreated areas at 28 weeks. There has been a slight extension of the neovascular complex.

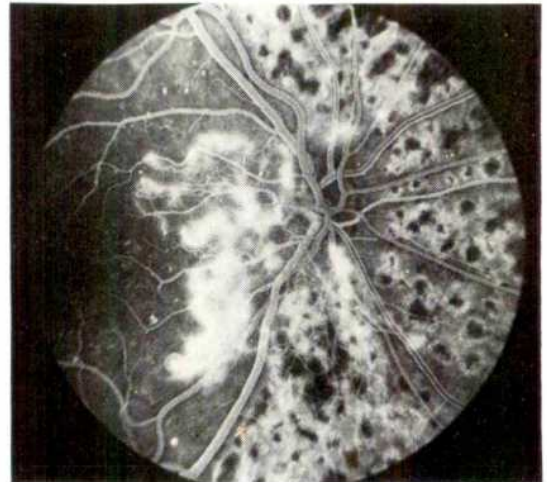


Fig. 6 Fluorescein angiogram showing the fundus of Fig. 4 6 months after successful completion of pregnancy. More extensive photocoagulation has been undertaken and there has been a slight reduction in neovascular tissue.

Table 3a Patients developing vitreous haemorrhage after cessation of photocoagulation therapy

	Pregnant	Nonpregnant	Men
Both eyes	4	10	9
Treated eye	2	5	5
Control eye	4	3	18
Absent	1	3	21
Total no. of patients	11	21	54

Table 3b Comparison of vitreous haemorrhage events in the female groups

	<i>Vitreous haemorrhage events (1 or more)</i>		
	<i>Present</i>	<i>Not present</i>	<i>P</i>
<i>Treated eyes</i>			
‘Pregnant’	7	4	0.0344
‘Nonpregnant’	5	16	Ho preg. Nonpreg.*
<i>Control eyes</i>			
‘Pregnant’	8	3	0.0396
‘Nonpregnant’	7	14	Ho preg. Nonpreg.*
<i>Pooled ‘pregnant’ eyes</i>	15	7	
<i>Pooled ‘nonpregnant’ eyes</i>	12	30	

*Ho preg. nonpreg. = pregnant not significantly greater than nonpregnant.

Table 4 Patients proceeding to blindness (<6/60 on the Snellen chart, at 2 successive 4-month visits) within 3 years

	Pregnant		Nonpregnant		Men	
	n	% Total	n	% Total	n	% Total
Neither eye blind	5	45.5	16	76.2	24	42.5
Treated eye blind	0	0	0	0	5	9.3
Control eye (only) blind	5	45.5	4	19	17	31.5
Both eyes blind	1	9	1	4.8	8	16.7
All untreated eyes blind	6	54.5	5	23.8	5	48.2

proceeding to blindness within 3 years was significant in all but the late stages of the proliferative process (McNemar's modified χ^2 test).

VISUAL ACUITY

No demonstrable significant difference between the retention of initial visual acuity in treated or control female eyes was demonstrated at any time (by Wilcoxon tests). When pregnant and nonpregnant patients were compared it was found that after 2 years there was a significant difference between the

treated eyes of the nonpregnant and pregnant groups. The mean cumulative deterioration of visual acuity was greater in the pregnant group. The same result was also seen at 2 years when the control eyes of the above 2 groups were compared (Fig. 7).

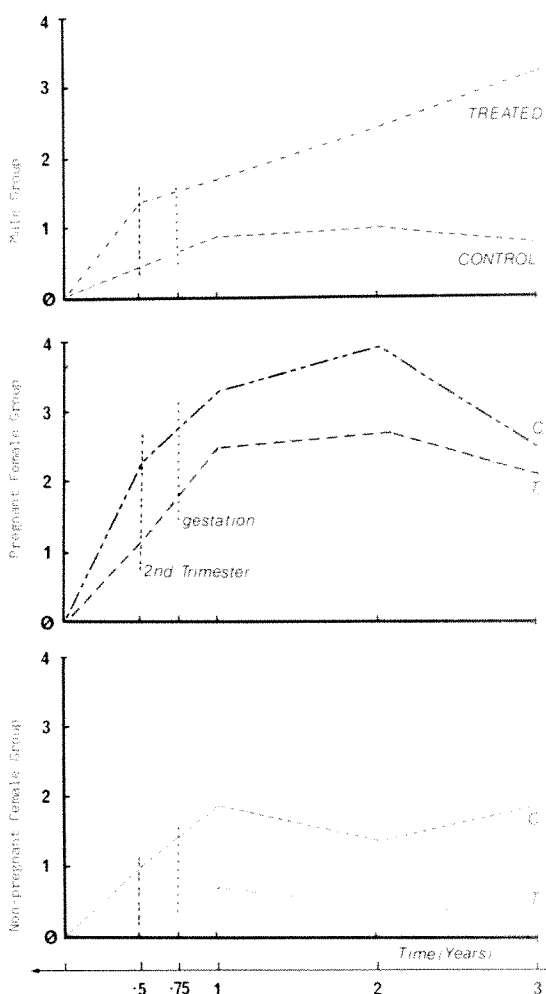
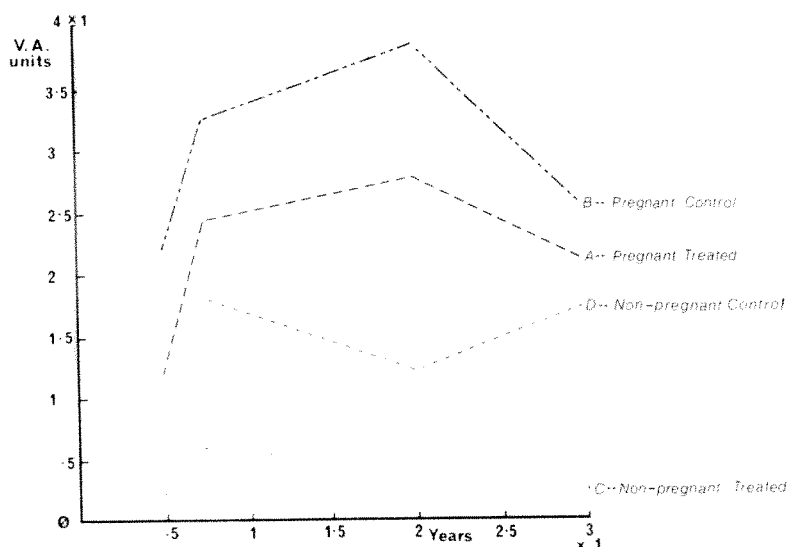


Fig. 7 Top: Three-year comparison of mean cumulative deterioration of visual acuity in male diabetics subjected to randomised uniocular panretinal photocoagulation for proliferative diabetic retinopathy involving the optic disc. Centre: Three-year comparison of mean cumulative deterioration of visual acuity between randomised eyes in pregnant diabetics (T=treated; C=control eyes). Bottom: Three-year comparison of mean cumulative deterioration of visual acuity in nonpregnant diabetic women subjected to uniocular, randomised, panretinal photocoagulation (nulliparous or more than 5 years regular menstruation prior to assessment).

Fig. 8 Mean cumulative deterioration of visual acuity contrast between all treated and control female eyes over the 3-year period following panretinal photocoagulation.



There was a statistically significant difference in mean cumulative deterioration of visual acuity between treated and untreated eyes (Table 5), in the female group studied (Fig. 8). This difference was found at all time-intervals measured, and is outlined below:

By Wilcoxon tests at	Between treated and control eyes
6/12	P=0.0297
9/12	P=0.0306
2 years	P=0.0025
3 years	P=0.0076

Discussion

No clear-cut conclusions regarding the effects exerted by pregnancy on proliferative retinal change in diabetes have been reached, because few centres have treated any significant number of patients, and the problem is further compounded by the fact that the natural history of the retinal process frequently spans a 9-month period. The outcome of pregnancy is certainly related, however, to the

presence of proliferative retinal change, as the severity of this change correlates quite closely with the presence of microangiopathy elsewhere in the body (especially the kidneys).⁷⁻⁹

It has not been possible clearly to elucidate an answer to the question, is pregnancy in some way exerting a trigger influence in the proliferative process? What does seem certain is that a considerable proportion of patients who show a progression of retinopathy during pregnancy will show regression after delivery.⁹⁻¹² Unfortunately, this is clearly not the case in the patients who show proliferative, as opposed to background, retinal changes. This is particularly true in the group presently discussed, where the proliferative changes are the most sinister and vision-threatening of all, because neovascularisation of the optic disc is present.

The present series has shown that, even with a peripheral retinal ablation procedure utilising between 1200 and 2500, 500 μ m spot-diameter impact-burns, a few beneficial effects are conferred. Significant improvement in neovascular status (>50%) at the optic disc occurred in 63.6% of cases. Yet this did significantly reduce the frequency of severe vitreous haemorrhage (≥ 2 lines fall, in visual acuity, on the Snellen chart). Again, no beneficial or protective effect occurred within 3 years, when eventual visual acuity was examined. There was evidence of a statistically significant difference in mean cumulative deterioration of visual acuity between treated and control eyes over 1-2 years.

Any woman with the retinal vascular problems ensuing from optic disc neovascularisation runs a

Table 5 Comparison of mean cumulative deterioration (between the 3 groups) of visual acuity at 2 years (Kruskal-Wallis analysis of variance)

		Group			
		1	2	3	
Treated eyes	n	10	12	42	P=0.0256 (poss. sig. diff)
	rank	19.3	39.25	33.7	
Control eyes	n	10	12	42	P=0.0966 (poss. sig. diff)
	rank	24.5	41.3	31.7	

grave risk in assuming the added metabolic burden of pregnancy. In the later stages, hypertension and albuminuria may first appear. It is at this point in the pregnancy when proliferative change may appear to be contained by photocoagulation. Yet such reduction in the progressive nature of this process seems to have conferred little benefit visually to the patients examined in this series. If pregnancy is permitted to run its course, scrupulous care is necessary for the successful management of the diabetic. It is thus worthwhile to pursue the potentially protective effects of panretinal photocoagulation with a more extensive form of application (up to 6000 impact burns) than described in the patients from this series. It is the authors' considered opinion that therapeutic abortion and sterilisation are not justified for ophthalmic reasons.

Our thanks are due to Dr E. S. Rosen and Mr A. Stewart Scott for their support and permission to treat patients in their care.

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Effect of preoperative posture and binocular occlusion on retinal detachment

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SUMMARY In an unselected series of retinal detachments a 24-hour period of binocular occlusion and posture with a retinal hole dependent produces some resolution of subretinal fluid in 13% of cases. If only patients with acute, freely mobile detachments and retinal holes above the horizontal meridian were selected the proportion of detachments showing some resolution rose to 30%. In 8% of cases a paradoxical response occurred, the detachment increasing in depth or extending to involve an additional area of retina.

The use of a period of preoperative posture and binocular occlusion is widely practised in retinal detachment surgery, but the exact indications and expectations for this manoeuvre are not well defined. Binocular occlusion decreases the frequency and amplitude of eye movements (Adams, *et al.*, 1973), and by this effect in combination with posture with the retinal hole dependent it is hoped to reduce the size of the detachment or at least prevent its further spread.

If this is possible, it may be helpful in the following ways: prevent macular detachment in cases where there is only peripheral detachment; enable more accurate localisation of a retinal hole by reducing the distance between the hole and the pigment epithelium; reveal a retinal hole hidden behind folds of ballooned retinal detachment; provide a view of the optic disc concealed by folds of detached retina; and settle a vitreous haemorrhage by allowing blood diffusely distributed in the retrohyaloid space to sediment inferiorly.

The resolution of subretinal fluid (SRF) that may occur after a period of bed rest is almost certainly not true reabsorption of SRF. Posture with the retinal hole dependent allows the retina to settle under the effects of gravity through the retrovitreal fluid, so that fluid which was initially subretinal becomes preretinal by transfer through the retinal hole (Foulds, 1975) (Fig. 1).

Apart from a recent review of the role of posture and binocular occlusion in the treatment of acute vitreous haemorrhage (Lincoff *et al.*, 1976) there have been a few recent studies of this form of

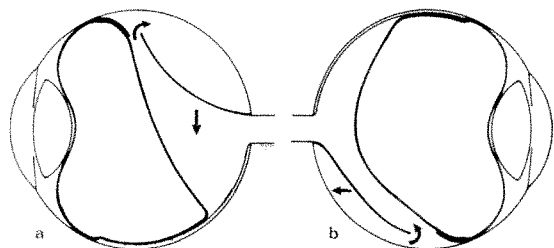


Fig. 1 (a) During the development of a ballooned superior retinal detachment the retina descends through the retrovitreal fluid. This fluid redistributes through the retinal tear from a preretinal to a postretinal position. (b) Posture of the patient with the retinal hole dependent allows reposition of the retina and transfer of fluid in the reverse direction

management in the context of current clinical practice. By means of fixation sutures in the medial and inferior recti it is possible to obtain some retinal flattening in 85% of patients (Algvere and Rosengren, 1977). Longer periods of rest and posture have a similarly high rate of success (Hoffman and Hanselmayer, 1973). However, such extensive preoperative preparation is rarely used in Great Britain, and this paper reports a prospective series of retinal detachments managed with a short period of preoperative posture. We undertook the study to assess the potential usefulness of this manoeuvre and formulate prognostic indicators for its successful application.

Materials and methods

A total of 100 patients were entered in this study. They were essentially consecutive, patients only

being exempted if an increased risk of thromboembolism precluded a period of immobility. For each patient the period of posture and binocular occlusion comprised the 24 hours immediately prior to surgery. The detachment was documented at the start of the period of bed rest and again just before operation. At the first examination 3 assessments were made: the topography of the detachment was documented and the depth of subretinal fluid was estimated in each retinal quadrant by scleral indentation and binocular indirect ophthalmoscopy. The depth of subretinal fluid was graded as; 0=flat; 1=neuroepithelium and pigment epithelium easily opposed by gentle scleral pressure with scleral indentation; 2=just appposable with scleral indentation; 3=unappposable despite scleral indentation. Thirdly the retinal mobility was assessed according to criteria previously described (Chignell, 1977). The patient was then positioned with the retinal hole dependent. If there were multiple and widely separated retinal holes, an attempt was made to decide the primary tear on the basis of the rules of fluid distribution (Lincoff and Gieser, 1971), and the patient was positioned appropriately. Both eyes of the patient were padded and treated with mydriatics and cycloplegics. The topography of the detachment and the depth of subretinal fluid in each retinal quadrant was then reassessed before starting surgery.

Results

CHANGE IN SRF

After 24 hours of posture and binocular occlusion 21 patients showed an apparent change in either the volume or distribution of SRF (Table 1).

In 13 patients the retina appeared to flatten. In another 4 patients the volume of subretinal fluid appeared unchanged but the topography of the detachment altered, so that an additional area of retina became detached. In 4 patients the volume of subretinal fluid appeared to increase and the detachment became more bullous. In 79 patients there was no detectable change. The type of retinal

Table 1 *Change in SRF in 100 cases of retinal detachment managed with 24 hours of posture and binocular occlusion*

Resolution	13
Redistribution	4
Increase	4
No change	79
Total	100

Table 2 *The behaviour of SRF related to the type of retinal hole in the 100 patients in this series*

	Alteration in volume of SRF	No alteration in volume of SRF	Total
U-tear/round hole	15	64	79
Dialysis	—	13	13
Giant tear	1	—	1
Macula hole	—	1	1
No tear found	1	5	6
Total	17	83	100

Table 3 *The behaviour of SRF related to the position of the retinal hole in 79 patients with identified equatorial retinal holes*

	Alteration in volume of SRF	No alteration in volume of SRF	Total
Upper 2 quadrants	13	32	45
Lower 2 quadrants	1	25	26
Both quadrants	1	7	8
Total	15	64	79

hole and its position were then analysed, as it seemed probable that these would influence the response to occlusion and posture.

TYPE OF RETINAL HOLE

In 17 patients there was an apparent alteration in the volume of the subretinal fluid. The distribution of types of retinal hole in the total series is given in Table 2.

Apart from 1 detachment in which no hole could be found, clinically detectable change in the volume of SRF occurred only in the presence of a definable equatorial or pre-equatorial retinal hole. The period of posture had no effect on any of the 13 detachments in this series owing to dialyses.

POSITION OF RETINAL HOLE

The position of the retinal hole was found to be crucial in predicting the behaviour of the detachment. Apart from those detachments caused by a dialysis, a giant tear, or those in which no hole could be found, there were 79 detachments with identified equatorial retinal holes. The response of detachments with superior tears is compared to those with inferior tears in Table 3.

Thirteen (29%) of patients with a superior retinal hole showed an alteration in the volume of subretinal fluid. Eleven (25%) patients showed a

decrease, and 2 showed an increase in the volume of SRF. An alteration in SRF, in both cases an increase in volume, occurred in only 1 case with an inferior hole and similarly 1 case with both superior and inferior holes. The 45 detachments with definable holes in the upper half of the retina therefore form the group in which change in SRF, either an increase or a decrease, can be expected. Three further factors were then analysed in this group alone:

Nature of retinal hole. We considered that a round hole where vitreous traction had been completely relieved by detachment of the operculum might be expected to settle more readily than a horseshoe tear where continuing though reduced traction on the operculum might limit its ability to gravitate through the retrovitreal fluid.

Refraction. We expected that the state of the vitreous gel and the size of the potential retrohyaloid space would affect the response.

Retinal mobility. We considered that the freedom of the retina to gravitate through the retrovitreal fluid would be adversely affected by retinal immobility.

NATURE OF RETINAL HOLE

The behaviour of detachments caused by horseshoe tears is compared to those which are due to round holes in Table 4. Five (56%) of those detachments caused by round holes showed an alteration in the volume of subretinal fluid, whereas 7 (27%) of those due to horseshoe tears showed an alteration in the volume of subretinal fluid. The total numbers are small, and this difference is not statistically significant ($0.10 > P > 0.05$), but it suggests that residual continuing traction on the retinal hole does not materially influence the volume of subretinal fluid.

REFRACTION

The distribution of refractive states within the group is given in Table 5. The difference in response of the myopic group 7 (29%) compared to the

Table 4 *The behaviour of SRF related to the type of retinal hole in 45 patients with retinal holes in the upper 2 quadrants of the retina*

	Alteration in volume of SRF	No alteration in volume of SRF	Total
Round holes	5	4	9
Horseshoe tears	7	21	28
Mixed	1	7	8
Total	13	32	45

Table 5 *The behaviour of SRF related to the refractive status in 45 patients with retinal holes in the upper 2 quadrants of the retina*

	Alteration in volume of SRF	No alteration in volume of SRF	Total
Emmetropia	2	10	12
Myopia	7	17	24
Hypermetropia	3	5	8
Aphakia	1	0	1
Total	13	32	45

Table 6 *The behaviour of SRF related to the retinal mobility in 45 patients with retinal holes in the upper 2 quadrants of the retina*

	Alteration in volume of SRF	No alteration in volume of SRF	Total
Mobile	13	24	37
Some mobility	—	7	7
Immobile	—	1	1
Total	13	32	45

combined emmetropic and hypermetropic group 5 (25%) is not significant ($P > 0.1$). Therefore refraction appeared not to be important, though the state of aphakia could not be assessed properly.

RETINAL MOBILITY

The presence of a freely mobile retina was found to be crucial to the response of posture (Table 6). Thus, all the detachments in which an alteration in the volume of SRF took place were freely mobile, but even with this favourable prognostic factor only 13 (35%) responded; 11 (30%) showed resolution.

INCREASED AREA OF DETACHMENT

Four of the 100 detachments in this series showed no apparent change in volume of subretinal fluid, but during the period of preoperative posture an increased area of the retina became detached. These 4 patients formed a heterogeneous group, but 3 of the 4 patients had upper-half retinal holes with freely mobile retinæ. In the remaining patient no hole was detected, but the retina appeared to be freely mobile.

Discussion

In 13 cases of this unselected series of 100 retinal detachments a 24-hour period of preoperative posture and binocular occlusion induced some

resolution of the subretinal fluid. In all these cases this facilitated localisation of the retinal holes at the time of surgery. In 1 case judged preoperatively suitable for surgical treatment involving drainage of subretinal fluid the reduction of SRF was sufficient to allow the optic disc to be viewed at surgery, and a nondrainage operation was performed. In 4 patients the detachment increased in area, and in an additional 4 patients an increase in the volume of subretinal fluid was found, but in none of these cases did this materially affect the outcome.

The disappointingly low number of positive responses to treatment in this series reflects the unselected nature of the detachments. The favourable prognostic factors which we have noted are a retinal hole above the horizontal meridian and a freely mobile detachment. If only detachments with these characteristics are compared, the proportion of patients showing resolution increases to 30%. No correlation was found with the type of retinal hole, and this suggests that continuing residual vitreous traction is not a major factor preventing resolution of SRF. However, larger numbers of patients are needed to confirm or refute this.

The failure of both inferior holes and dialyses to respond to preoperative bed rest suggests that the flattening of a detachment when it occurs is due to a gravitational settling of the retina and not true reabsorption of SRF. With inferior holes the detachment has already developed despite the effect of gravity tending to reposition the retina. In a dialysis the vitreous base remains attached to the posterior edge of the retinal hole (Scott, 1977); no passage exists for transfer of fluid from the subretinal to the preretinal space, and the retina is thus unable to gravitate through the retrovitreal fluid by displacing fluid from one compartment to another. Perhaps this explains the universally poor prognosis for bed rest with this type of retinal hole.

The results of this study crystallise the day-to-day impression of retinal surgeons that acute, freely mobile retinal detachments with holes above the horizontal meridian have the most favourable prognosis for response to preoperative posture. Furthermore it is important to recognise that in this group a small proportion will increase in depth. In a further small proportion of cases,

although the volume of subretinal fluid appears unchanged, a larger area of retina becomes detached. The explanation of this paradoxical increase in either the depth of subretinal fluid or area of detachment is not clear. It probably represents a failure of the patient to maintain correct posture and confirms the labile nature of this type of detachment. Clinically it cautions against assuming axiomatically that a retinal detachment will not extend once the patient is put to bed.

However, even with these favourable prognostic indications only 30% of detachments were improved. Confirmation of this proportion has been obtained in a further group of patients. Using the criteria derived from this study we have continued to advise bed rest only for those patients with freely mobile upper-half detachments. Thirty-one of the subsequent 150 detachments fulfilled these requirements, of which 8 (26%) responded to a short period of bed rest.

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Buckling procedures for retinal detachment caused by retrolental fibroplasia in premature babies

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SUMMARY Three premature babies with advanced stages of retrolental fibroplasia underwent retinal surgery by buckling procedures, with satisfactory results. The indications and surgical technical problems are discussed.

Retrolental fibroplasia (RLF) is not infrequently diagnosed today, despite our increasing knowledge of its pathogenesis. For years the main aim of ophthalmologists was directed toward the prevention of this disease by restriction of oxygen therapy. It is only recently that surgical treatment of the active stages of RLF has been reported. The treatments included argon laser and xenon arc photocoagulation (Oshima *et al.*, 1971; Payne and Patz, 1972; Nagata and Tsuruoka, 1972; Vemura, 1975; Yoshida *et al.*, 1975; Tsumura *et al.*, 1976; Soejima *et al.*, 1976) and cryopexy (Payne and Patz, 1972; Harris, 1976; Kingham, 1977).

There is no well established policy for treating active RLF, and the indications for such treatment have not been clearly defined. Payne and Patz (1972) applied argon laser photocoagulation and cryopexy in cases showing active progressive proliferative disease and significant vitreous haemorrhage, and others have been using these forms of treatment in similar cases, including ourselves who, since 1975, have treated 25 cases with progressive active proliferation by cryopexy.

The severe forms of the cicatricial stages, where traction retinal detachment and dragging of the optic discs and vessels exist, afford a great challenge to the surgeon and we are not aware of any published report dealing with the surgical correction of this form of retinal detachment in premature babies. In this report we shall describe in detail the surgical procedures and results in 3 cases with advanced cicatricial RLF, including traction retinal detachment, where the retinae were successfully reattached by buckling procedures.

Case reports

CASE 1

A premature baby boy, born after a 28 weeks pregnancy, weighing 1000 g, received oxygen therapy for 43 days because of respiratory distress syndrome. The maximal oxygen concentration was 80% and the maximal Po_2 measured was 241. Retrolental fibroplasia was diagnosed at 2 months of age. The baby did not follow light, and nystagmoid movements were observed.

In the left eye a total traction retinal detachment was found and considered inoperable at that time—cicatricial stage V according to Patz's classification (Patz, 1969). In the right eye a traction retinal detachment was found, starting at the temporal periphery, including the macula and extending up to the disc, with some active neovascular proliferation (cicatricial stage IV).

A local buckling procedure was performed on the right eye. This consisted of an invaginated lamellar flap of sclera rolled on itself (Stallard, 1973), (Fig. 1). This flap was two-thirds the thickness of the sclera and was located around the equator temporally from 1 to 6 o'clock. Cryotherapy was applied to the detached area. No release of subretinal fluid was performed. The retina reattached immediately postoperatively, except at the extreme temporal periphery.

In a follow-up examination 3 years after this procedure the boy showed good fixational reflexes and no nystagmus. He could perform normal visual tasks using his right eye only, which was -13.00 D. The fundus showed a subalbinotic myopic flat retina with a buckle on the temporal side, the retina anterior to the buckle showing a shallow

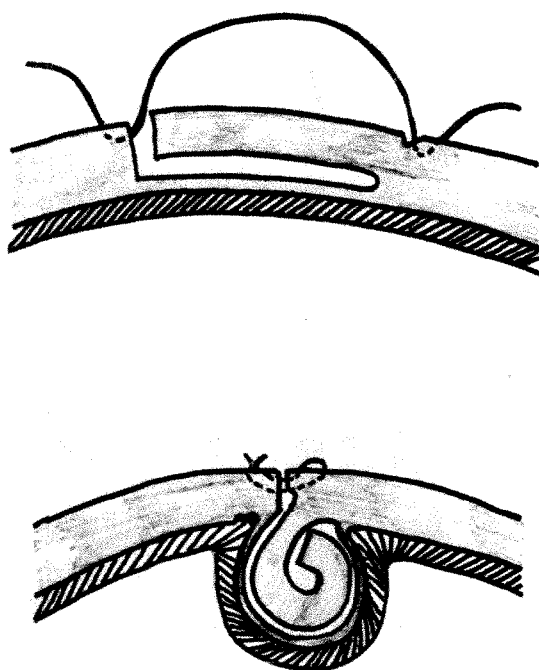


Fig. 1 Buckling procedure by an invaginated lamellar flap of sclera rolled on itself

detachment. A good macular reflex was observed. The angle between the temporal vessels of the disc was 100° , and a number of pigmented chorioretinal scars in the area of the previously detached retina could be seen. The left eye showed a total retinal detachment with a retrolental mass.

CASE 2

This premature baby, born after a 31 weeks pregnancy, weighing 1650 g, received oxygen therapy for 6 days because of respiratory distress syndrome. The maximal oxygen concentration was 50% and the maximal Po_2 measured was 118.

Active proliferative and cicatricial stage III disease was first detected at the age of 10 weeks and was found in both eyes. A thick active proliferative fibrovascular ridge was seen in the temporal

periphery with retinal and vitreous haemorrhages, causing a marked dragging of the vessels of the optic disc, with an angle of 80° between the temporal vessels and a shallow retinal detachment in the temporal periphery. Cryopexy was performed in the temporal periphery of both eyes. Two weeks later the right eye showed an arrest of the proliferative process with pigmented chorioretinal scars temporally.

In the left eye a total retinal detachment was found. A buckling procedure was performed on this eye, consisting of an equatorial encircling Lincoff sponge of 1.5 mm, with release of subretinal fluid. The retina flattened immediately postoperatively. One month after this procedure the retina was flat, with a moderate buckling effect all around. Dragging of the vessels of the disc (80° angle) and macula persisted. The right eye, which only underwent cryopexy, showed a more marked dragging of the disc with an angle of 50° between the temporal vessels and a heterotopic elongated macular reflex.

At a follow-up examination 18 months after surgery the child's fixational reflexes in each eye were normal, and no nystagmus was seen. Refraction in the right eye was -6.0 D and in the left eye -10.0 D. The child seemed to have good vision in both eyes. The ophthalmological picture remained unchanged.

CASE 3

This premature baby, born after a 30 weeks pregnancy, weighing 1280 g, received oxygen therapy for 8 days. The maximal oxygen concentration was 40% and the maximal Po_2 measured was 150.

Active proliferative disease was first detected when the baby was 2 months old. The left eye showed a thick fibrotic vasoproliferative band with retinal and vitreous haemorrhages in the temporal periphery, causing an elevated traction retinal detachment comprising two-thirds of the retina. Surgery was performed on this eye in order to stop the neovascular proliferation and to treat the traction retinal detachment. The surgery consisted of a local buckling procedure with a Lincoff sponge 1.5 mm wide, located along the equator from the 10 to 8 o'clock meridia, and cryopexy to the tem-

Table 1 Background data of the 3 reported cases

	Weeks of pregnancy	Birth weight (gm)	Age at diagnosis (days)	Days in oxygen therapy	Highest incubator O_2 concentration	Highest Po_2 measured
Case 1	28	1000	60	43	80%	241
Case 2	31	1650	75	6	50%	118
Case 3	30	1250	60	8	40%	150

poral retina. No release of subretinal fluid was performed, and the retina flattened postoperatively. In follow-up examinations up to 12 months later the eye showed an attached retina, a moderate buckle with less dragging of the vessels of the optic disc and macula, and a number of pigmented chorioretinal scars.

At the first examination the right eye showed marked traction of the temporal retina, causing dragging of the disc with an angle of 100° between the temporal vessels. There was an abnormal macular reflex and a shallow retinal detachment temporally. One month after this examination a further narrowing of the angle of the vessels to 80° was noticed, while the area of detached retina remained unchanged. Ten months later the retinal detachment disappeared spontaneously, but the marked traction on the disc and macula remained.

Discussion

The main process that leads to the formation of retinal detachment in cases of acute and cicatricial RLF is the formation of a thick fibrovascular band in the temporal half of the peripheral retina. The contraction of this band produces a marked traction on the retina, causing dragging of the vessels of the optic disc, heterotopia with elongation of the macula, and a traction retinal detachment. This traction retinal detachment can appear with the regression of the vasoproliferative stage or some years later.

We believe that it is important to prevent the formation of the fibrovascular band in cases showing progression of the neovascular process. Cryopexy over the new vessels and the avascular peripheral retina produces a complete regression of neovascular activity. This procedure may prevent the development of retinal detachment in later years. In our experience cryopexy is a safe and effective method of treatment, though a longer follow-up period is necessary before final conclusions can be reached.

A shallow retinal detachment in RLF can reattach spontaneously. When a high traction retinal detachment is present (cicatricial stages IV and V), it is our experience that spontaneous regression is no longer possible, and the same criteria for treatment which are applied in cases of retinal detachment in adulthood should be considered. A prompt attempt to flatten the detachment is mandatory, for damage to the retinal neuronal structures depends directly upon the time elapsing until a reattachment is obtained, either spontaneously or by surgical means.

This time factor is particularly important when dealing with a retinal detachment of the macular

area, and for this reason we performed surgery in those cases where a spontaneous rapid reattachment did not occur. A local buckling procedure by an invaginated lamellar flap of sclera has several advantages: a circumferential shortening of the eye, a local indentation under the detached retina, and a decrease in the ocular volume are obtained by this technique, without causing a marked constriction of the growing eye. Since no foreign materials are used, the dangers of extrusion, infection, and ocular penetration are minimal. Whenever possible an encircling buckling procedure was avoided, since the effects of such a constricting foreign body on the growing eye are not known. An encircling procedure was performed in case 2 because we believed that a local buckling procedure would not be sufficient to alleviate the marked traction on the retina. In this case we suspected that the detachment was caused both by an exudative process and by traction. When after 2 weeks we did not observe any tendency to reattachment, we proceeded with surgery.

Retinal surgery in small babies presents several technical difficulties. The relatively small volume of the orbits in comparison with the size of the eyeball may produce serious difficulties when trying to work on the equatorial area or posterior to it. The implantation of foreign material into the relatively small orbits may increase temporarily the intraocular pressure and, if not carefully monitored, may lead to closure of the central retinal artery. Another serious technical problem results from the thin sclera of these premature babies, which may present difficulties with regard to intrascleral procedures.

In the 3 cases presented the retina was reattached successfully immediately after surgery, and remained attached in follow-up examinations. Although accurate determination of visual acuity is impossible at this age, all the children can perform normal visual tasks with the eyes that underwent surgery. Only a long follow-up period will show if this kind of surgery in premature babies is effective in the long term. It is still to be determined whether such buckling procedures prevent later development of traction retinal detachment, a common complication in the first and second decades of life in children with RLF.

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Epiretinal membrane formation associated with spontaneous massive periretinal proliferation

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SUMMARY A 74-year-old man with cardiovascular disease and epiretinal membrane formation developed spontaneous massive periretinal proliferation over a period of 3 months. No surgery was performed at any stage. A 3-year follow-up is described and theories concerning the production of these 2 entities are discussed.

Epiretinal membrane formation is not uncommon in an older population, appearing first as a glistening reflex from the surface of the retina, more easily seen in red-free light (Wise, 1975). As the membrane thickens and retracts, superficial retinal folds appear and macular pucker can occur. Massive periretinal proliferation, formerly called massive vitreous or preretinal retraction, may follow operations for retinal detachment.

The following case history describes a continuing process of epiretinal membrane formation leading to spontaneous massive periretinal proliferation without any surgical procedure being performed.

Case report

A 74-year-old man suffering from cardiovascular disease presented with deterioration of vision in his left eye. On examination visual acuities were 6/9 right and 6/36 left, with a spectacle correction. The right eye was normal, but the left showed several flame-shaped haemorrhages near the optic disc margin, with an epiretinal membrane over the central area, giving the appearance of oedema (Fig. 1). No vitreous cells, pigment, or detachment were present. Fluorescein angiography showed early leakage of fluorescein from the disc and temporal vessels and some staining of the vessel walls (Fig. 2).

The patient was seen at intervals, and some 3 months after the initial consultation he presented with a history of loss of vision in his left eye of 2 days' duration. On examination visual acuities were 6/6 right, hand movements left. The vitreous showed

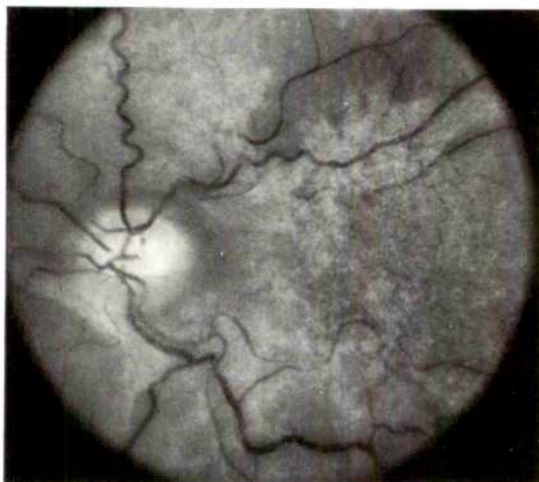


Fig. 1 Red-free photograph showing central epiretinal membrane

a large number of pigment clumps just anterior to an extensive retinal detachment. The retina showed greyish folds with 2 tears in the upper temporal quadrant (Fig. 3). The patient declined operation, and over the next few days the retina rapidly contracted into a funnel-shaped retinal detachment showing the typical appearance of periretinal proliferation (Fig. 4).

Over a period of 1 year there was considerable large pigment clumping behind the lens in the region of the ligament of Wieger and just in front of the retina. A complete membrane existed across the retina, including the central funnel leading to the optic disc, which could not be clearly seen. The original retinal tears had contracted and were covered by a membrane containing new vessels.

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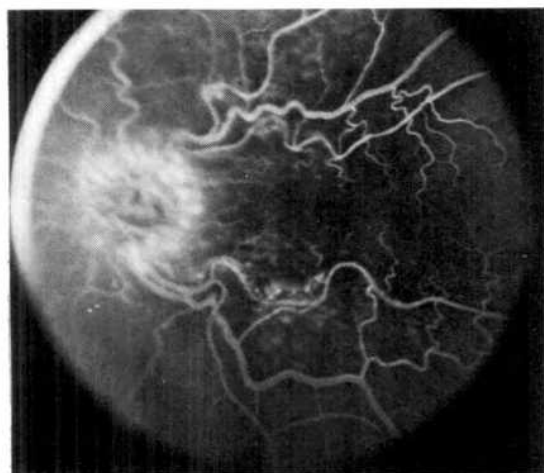


Fig. 2 Fluorescein angiogram showing early leakage of fluorescein from the disc and temporal retinal vessels and some staining of the retinal vessel walls

Two years after the onset of the massive periretinal proliferation the pigment began to disappear. After 3 years vision was no perception of light in the left eye, and the pigment at the back of the lens and on the retina had practically disappeared. The membrane over the funnel leading to the optic disc had retracted, and the optic disc could now be seen. The original retinal tears in the upper temporal quadrant were obscured by fibrous tissue across the surface, but the new vessels were still present.

Discussion

Epiretinal membrane formation has been thought to follow cell proliferation. This proliferation may be from retinal pigment epithelial cells (Machemer and Laqua, 1975) or Muller cells and haematogenous macrophages (Gloor and Daiker, 1975) or astrocytes (Foos and Gloor, 1975). Inflammation may also be a factor, and in some cases epiretinal membrane formation may follow vasculitis. Breaks in the inner limiting membrane of the retina have been implicated (Foos, 1972).

The present case shows that epiretinal membrane formation and periretinal proliferation can form a continuous process. The opinion that spontaneous retinal pucker never leads to massive periretinal proliferation is not correct on the evidence of the present case (Machemer, 1978). It is of interest that the patient did not develop pigment in the vitreous until the stage at which the retina was detached and in fixed folds.

It would appear that if there is enough fibro-

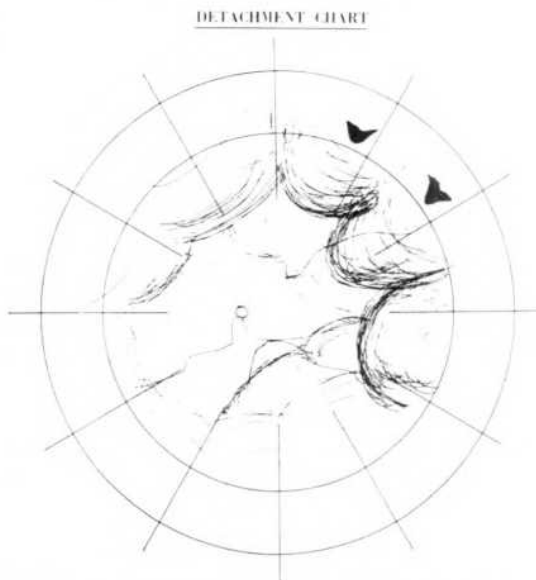


Fig. 3 Fundus drawing showing retinal detachment with folds and 2 tears in the upper temporal quadrant

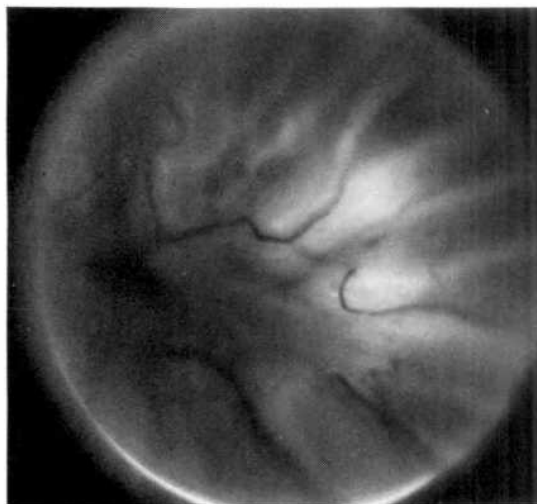


Fig. 4 Fundus photograph showing a funnel-shaped retinal detachment typical of periretinal proliferation

cellular proliferation on the surface, then the retina is capable of being rucked up and retinal tears can be produced. The role of vitreous contraction in this process is uncertain, and in the present case a posterior vitreous detachment was not present at any stage, so that any vitreous contraction could directly affect the retina.

I am grateful to Dr C. N. Banks for his original referral of the case, Dr Paul Mitchell for performing the fluorescein

angiogram, and Mr Ken Deason and the staff of the Medical Illustration Department of the Prince of Wales Hospital, Randwick, for the illustrations.

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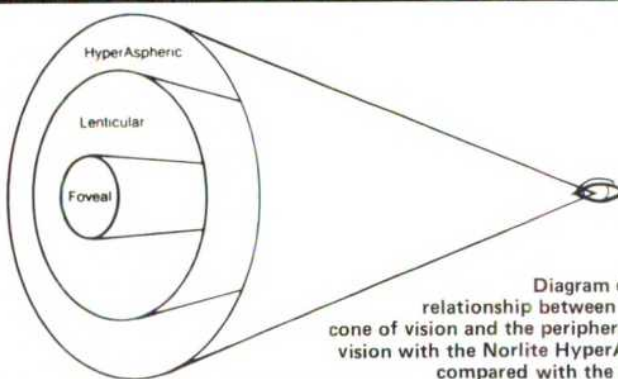


Diagram defines the relationship between a patient's cone of vision and the peripheral cones of vision with the Norlite HyperAspheric as compared with the lenticular.

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Posterior hyperplastic primary vitreous

K. RUBINSTEIN

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SUMMARY A fundus picture of posterior hyperplastic primary vitreous based on a study of 14 cases is described. Its definition, in spite of pleomorphic manifestations, could be useful for its differentiation from other conditions affecting children's eyes and presumed to be caused by parasitic, inflammatory, fibroplastic, or genetically transmitted processes.

The basic role of persistent hyperplastic primary vitreous in the aetiology of tunica vasculosa lentis and its complications has been well established for nearly a century. Ample histological material was provided as children's eyes were being enucleated because of an erroneous diagnosis of retinoblastoma. In 1935 Ancona (1935), Mann (1935), and Weve

(1935) reported on congenital falciform retinal folds (ablatio falciformis retinae, congenital retinal septum), and Mann (1935) advanced a concept—based on embryological studies—of the basic aetiological role of persistent primary vitreous in this condition too. Mixed cases were found in which both anterior and posterior segments seemed to be involved, and the reports were the subject of scholarly review by Reese (1955) in his Jacksonian lecture. The responsibility of hyperplastic primary vitreous for the causation of certain retinal holes

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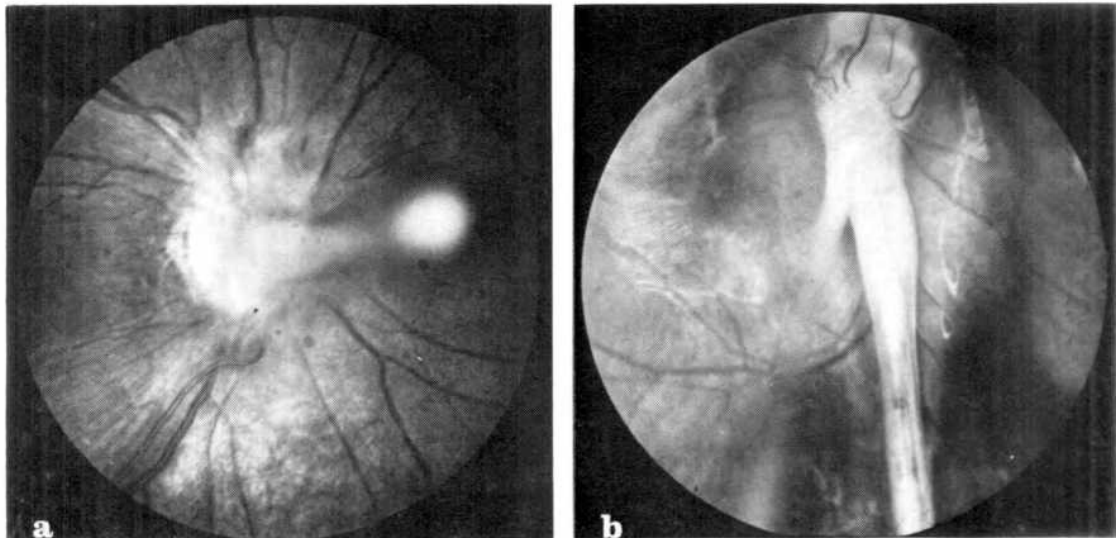


Fig. 1 Case 1. a. The right eye of a 7-year-old girl seen 4 years ago. Visual acuity 6/18. Glial tissue partly covers the optic disc and extends as a strand up and nasally to end in a white, hazy knob at the surface of the retina. The macula (not in the picture) showed cystic degeneration and tension striae towards the disc. b. The same eye 4 years later. Visual acuity 6/36. Marked increase in elevation of glia at the disc. A thick fold now stretches from the disc downwards carrying retinal vessels. Nasally several fine linear strands are seen (? primary vitreous), as well as deep pigmentary disturbance.

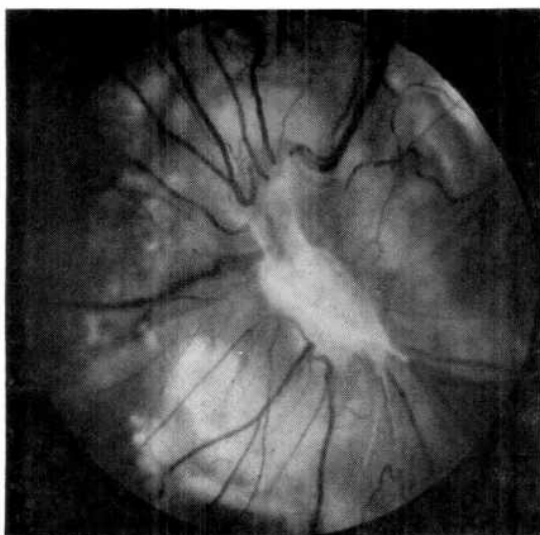


Fig. 2 Case 2. The left eye of an 8-year-old boy. Visual acuity 6/36. The optic disc is shapeless; its true outline is seen only at the 12 o'clock meridian. A white saucer-like plaque extends from there down and temporally. The blood vessels form hairpin bends and arcades. Deep pigment dystrophy and abnormal deep glial tissue is seen

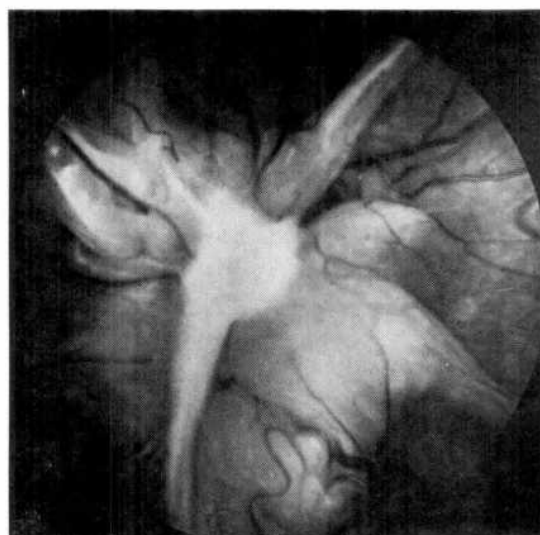


Fig. 3 Case 3. The left eye of a 6-year-old boy. Visual acuity counting fingers. A ragged white deposit is nearly totally masking the optic disc. Two folds extend from it downwards and upwards towards the periphery. Temporally the retina is pulled forwards; a similar but lesser pull is seen at the 10 o'clock meridian. The vessels are tortuous and form hairpin bends

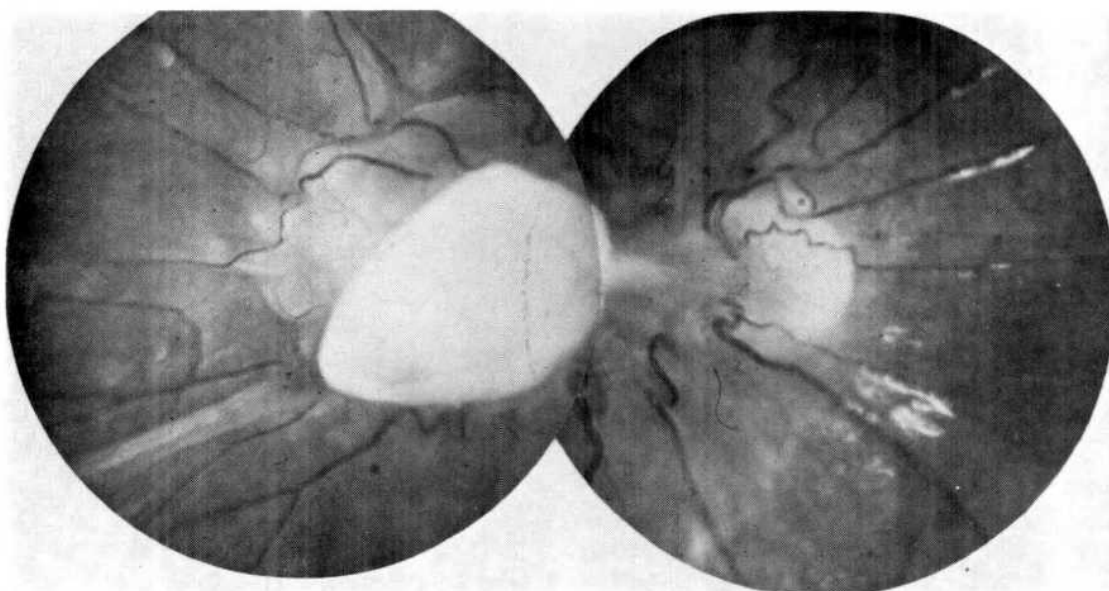


Fig. 4 Case 4. The right eye of a 5-year-old boy. Visual acuity perception of light. A dense, ovoid, saucer-shaped plaque covers the macula. The blood vessels are distorted and stretched. They form hairpin bends. Tension folds radiate towards the inferotemporal periphery. The optic disc is partly covered by glial tissue, which merges temporally with the macular plaque. It shows no physiological cupping and is flesh coloured. Along the stretched blood vessels are glistening white tissue strands (? primary vitreous)

and retinal detachments was suggested by Hagedorn and Sieger (1956) and Pruett and Schepens (1970).

The presence of abnormalities in the posterior segment of the eye, even without the anterior segment being affected, was established by Manschot

(1958) and Wolter and Flaherty (1959) as a result of careful histological studies. Pruett (1975), reviewing his clinical material from 30 patients (33 eyes), stressed the variety of fundus lesions. The following clinical features were found in his series:

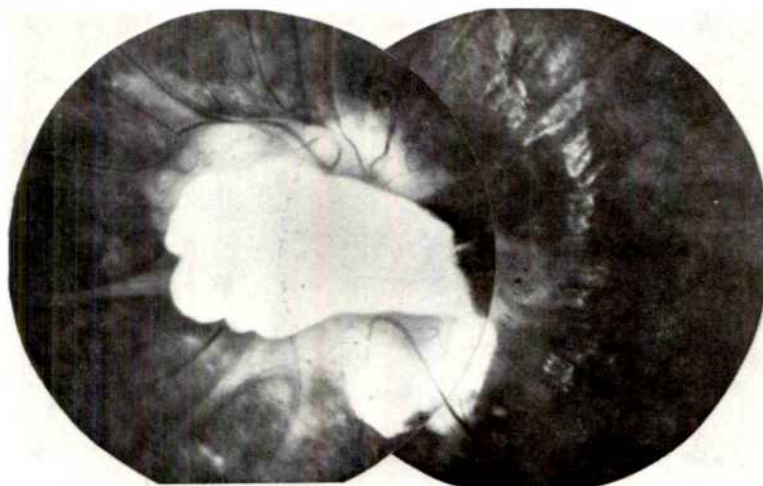


Fig. 5 Case 5. The right eye of a 6-year-old girl. Visual acuity counting fingers. A fist-like, dense white band arises from the optic disc and extends over the macula, with starfish folds radiating temporally. The blood vessels are tortuous and form arcades. Nasally there is a concentric halo of streaky glistening deposits (? primary vitreous)

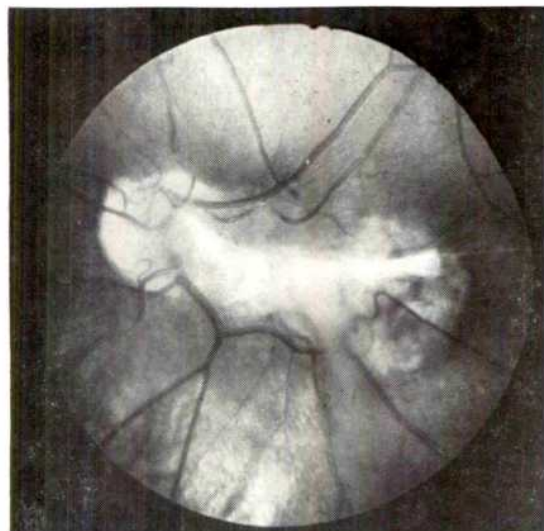


Fig. 6 Case 6. The left eye of a 10-year-old girl. Visual acuity perception of light. The optic disc is flesh coloured, and shows no physiological cupping. A veil-like band of white-greyish tissue covers its temporal part and extends and runs over the macula, where it ends. The macula shows a pigment clump surrounded by a depigmented halo. The blood vessels form scalloped arcades and hairpin bends. Inferiorly the retina shows a metallic reflex (? primary vitreous)

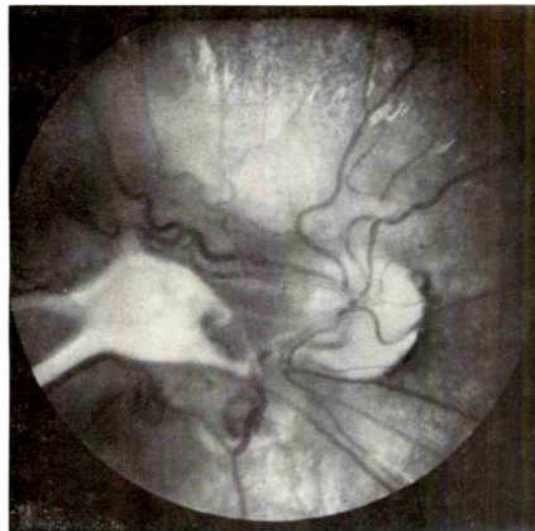


Fig. 7 Case 7. The right eye of a 5-year-old girl. Visual acuity 6/60. The optic disc is of flesh colour and shows no physiological cupping. From it a fold of elevated retina reaches the macula, which is masked by a ragged plaque of white tissue, with spiky extensions from its temporal edge. The blood vessels show tortuosity superiorly and are stretched inferiorly. A fine glistening pattern is seen in the upper periphery of the picture (? primary vitreous), and a patch of deep pigment disturbance below the disc

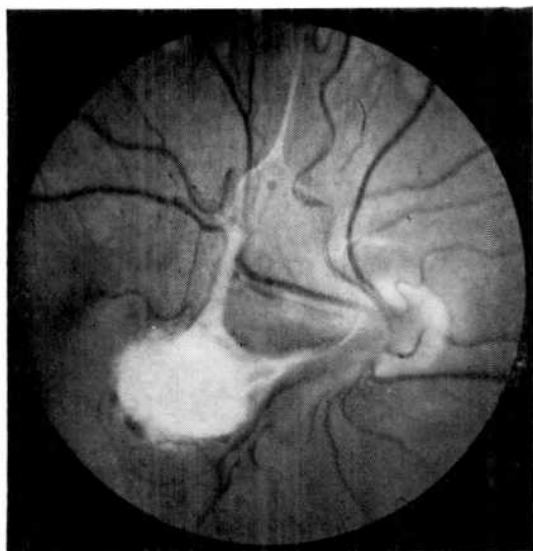


Fig. 8 Case 8. The right eye of an 18-year-old girl. Visual acuity 6/60. From a distorted, flesh coloured, and ill-defined disc strands of white veil-like tissue reach the macula, where they terminate as a furry, dense, white knob. From there similar strands and veils extend upwards. They are preretinal but posterior to the vitreous and not elevated, and they distort and pull the retinal vessels with them. Fluorescein angiography showed a glow from the optic disc

retinal detachment, 15 eyes; macular pigmentation, distortion, and involvement by a fold, 23 eyes; vitreous haemorrhage, 1 eye; glaucoma, 1 eye; cataract, 2 eyes. As these children were referred to the Boston Retina Unit, internationally reputed for its retinal detachment work, the referrals were likely to have been selective.

The present report is based on 14 cases seen during the past 8 years in the diagnostic angiography unit, which by its nature did not attract the referral of patients affected by retinal detachment or anterior segment lesions. The clinical picture which emerged from our study is presented to help in the diagnosis of persistent posterior hyperplastic primary vitreous (PHPV), which may be difficult in view of pleomorphic and often bizarre manifestations of its presence.

Patients and methods

Of the 14 patients 8 were male and 6 were female. Their ages when they were first seen were between 5 and 25 years (11 patients 5–10 years, 3 patients 15–25 years). In 13 cases only 1 eye was affected; in 1 case the other eye was affected to a lesser degree (case 14).

The reasons for primary referral to an ophthalmologist were poor unocular vision or a squint. The levels of visual acuity (15 eyes) were as follows:

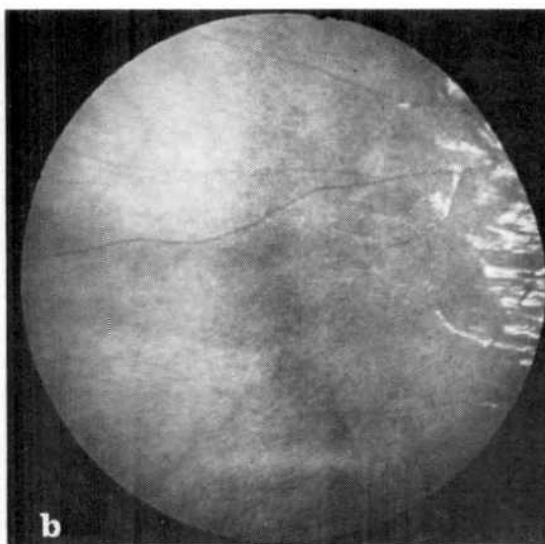
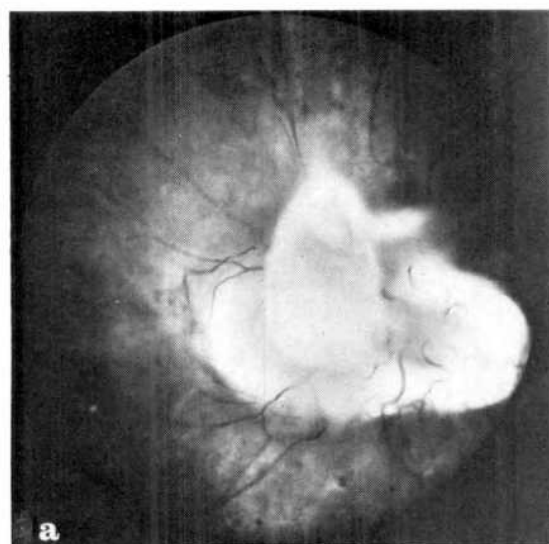


Fig. 9 Case 9. The right eye of a 10-year-old boy. Visual acuity hand movements. a. The optic disc consists of a white, wide rim seen only on the nasal side and a small, central, flesh coloured core. It is continuous temporally with a similar rim of slightly larger diameter to form an oval saucer which encompasses the macula and disc. From the centre of this saucer arises a grey-whitish cone of glia. The periphery shows widespread deep pigmentary disturbance. b. The far periphery shows glistening linear deposits (? primary vitreous)

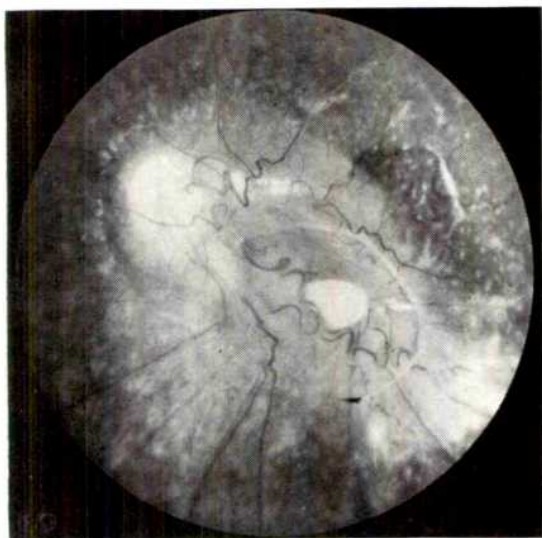


Fig. 10 Case 10. The left fundus of a 6-year-old boy. Visual acuity perception of light. The disc-macula complex is difficult to localise with precision because of gross distortion of all central retina by flat preretinal bands. There are dense, white deposits, the lower one probably at the macula. The blood vessels form hairpin bends; some are tortuous, and some are stretched into narrow, straight course. The periphery shows widespread deep pigmentary disturbance. The other eye has 6/6 vision; its fundus showed marked tortuosity of vessels only

Fig. 11 Case 11. The left eye of an 8-year-old boy seen 7 years ago. Visual acuity counting fingers. a. The outline of the disc is lost under a thick preretinal membrane and glial deposits. The disc is flesh coloured. The central vessels are tortuous and form hairpin bends. A thin fold-like band runs from the disc up and nasally. From a dense tulip-like deposit on the temporal side of the disc another band runs out and temporally. This temporal band thins out and spreads to end below the raphe

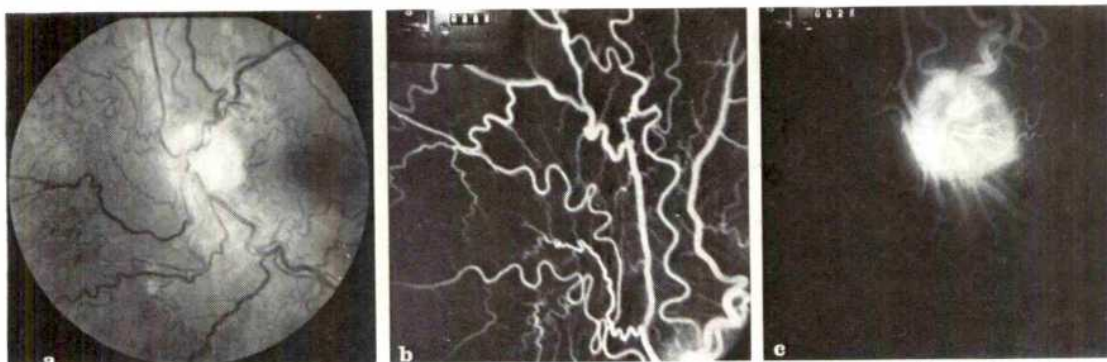
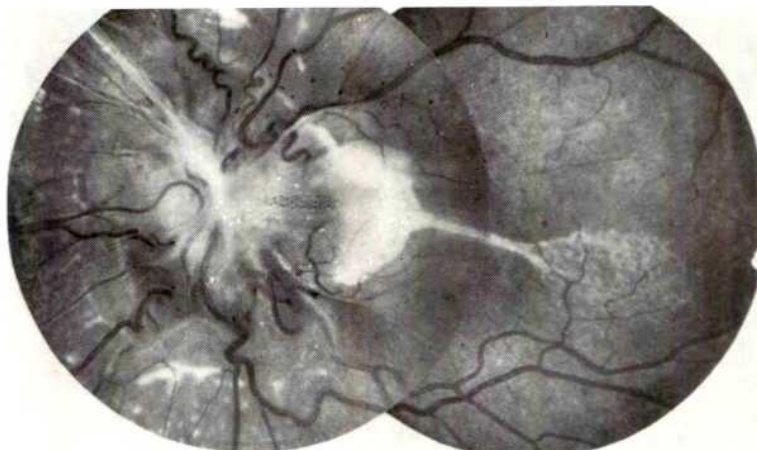


Fig. 12 Case 12. The left eye of a 10-year-old girl. Visual acuity counting fingers. a. The optic disc is distorted, shows no physiological cupping, is flesh coloured, and has a hazy outline. The blood vessels show marked tortuosity, uneven calibre, and crowding. The macula is covered by a membrane. b. Fluorescein angiography shows that in spite of gross tortuosity there are no leakages from the blood vessels. c. The optic disc shows marked late stain typical for glial and fibrous tissue

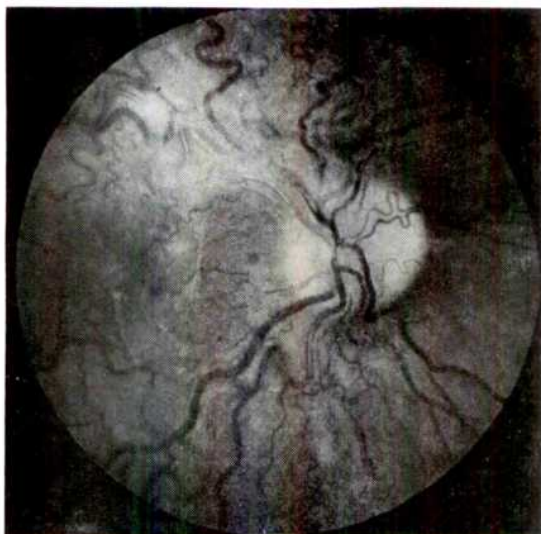


Fig. 13 Case 13. The right eye of a 25-year-old man. Visual acuity 6/60. The optic disc shows flesh colour, no physiological cupping, and its outline is defined only on the nasal side. Superiorly the blood vessels are tortuous, distorted, and unevenly covered by a preretinal membrane. This membrane extends over the macula. Fluorescein angiography showed late stain of the optic disc

6/9, 1; 6/18–6/60, 6; counting fingers to perception of light, 8. All fundi were photographed, but fluorescein angiography could not be performed efficiently in most patients because of their age. In fact only 6 patients had this test. All were investigated for parasitic, inflammatory, and autoimmune disease, with negative results. In no case did we find any of the features characteristic of anterior segment involvement—for example, microcornea, angle abnormalities, cataract, retrolental membrane, cloudy vitreous, glaucoma. No eye was inflamed, irritable, or photophobic.

Results

The legends of Figs. 1–14 describe the pathological findings in individual cases. The incidence of salient features is summarised in Table 1. Many individual features were present simultaneously in affected eyes. However, the dominating features for the series can be established.

Thirteen cases were unilateral (93%). The optic disc was severely affected in all of them by distortion, loss of outline, absence of physiological cupping, and fleshy disc colour. 53% of the eyes showed radiating folds and bands, and 47% showed gross involvement of the disc-macula complex by heavy

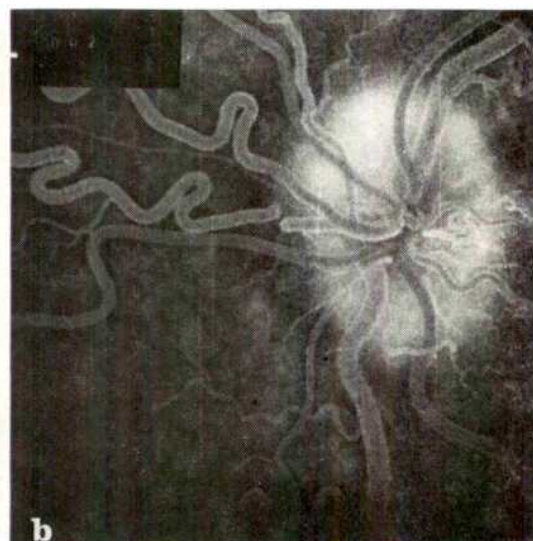
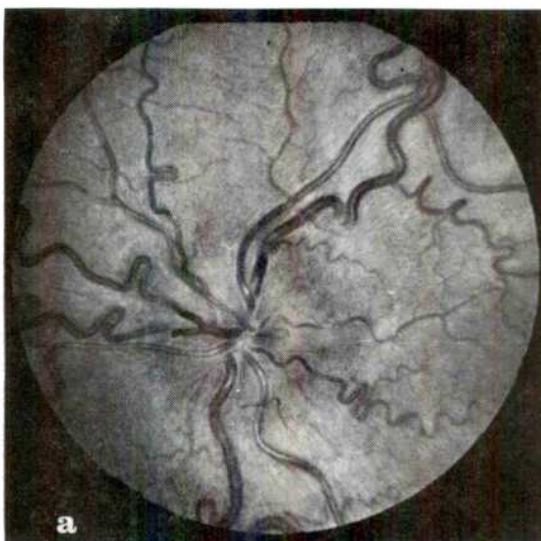


Fig. 14 Case 14. The left eye of a 15-year-old boy. Visual acuity 6/18. a. The blood vessels are markedly tortuous. At the 11 o'clock meridian several small vessels are stretched in the horizontal direction, ladder-like. The superior temporal vein is covered by a grey membrane just above the disc. The macula is covered by a grey thin membrane, and above it the blood vessels are markedly scalloped, forming arcades. The optic disc is poorly defined, fleshy, and shows no physiological cupping. The other eye showed nearly symmetrical changes, but the macula was free of membrane, with vision 6/9. b. Fluorescein angiography shows no leakages from blood vessels but late glow of the optic disc

Table 1 Incidence of individual features (15 eyes)

Disc		
Distortion, loss of outline	15	100%
Absence of physiological cupping	15	100%
Fleshy colour	15	100%
Glial proliferation	11	73%
Radiating folds and bands	8	53%
Gross disc-macula deposits	7	47%
Late fluorescence	all 7 tested	
Macula		
Preretinal membrane	10	67%
Glial deposits	7	47%
Cystic degeneration	4	27%
Pigment dystrophy	4	27%
Displacement	2	13%
Vessels		
Distortion	13	89%
Tortuosity	12	80%
Hairpin bends	8	53%
Periphery		
Deep pigment disturbance	9	60%
Glistening deposits	6	40%

deposits of glial tissue. All 6 cases which had fluorescein angiography showed marked, late fluorescence of the disc, case 14 in both eyes.

The maculae were affected secondarily in all cases by premacular membrane, glial deposits, pigment dystrophy, or cystic degeneration. The retinal blood vessels were distorted, tortuous, and formed hairpin bends in all cases. It is interesting that in 6 cases (40%) peripheral glistening deposits were seen,

some similar to those reported by Pruett (1975). Deep pigment disturbance outside the macular area was seen in 60% of cases.

Discussion

These observations indicate a pleomorphic fundus syndrome caused by the persistence of primary hyperplastic vitreous in the posterior segment of the eye. The occurrence of retinal detachment, as reported previously by other workers, has to be incorporated to make the syndrome complete. The differential diagnosis is between retrolental fibroplasia, parasitic infections, inflammatory conditions, and congenital vascular abnormalities of the retina.

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Autosomal dominant exudative vitreoretinopathy

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SUMMARY Twelve affected members from 3 families with autosomal dominant exudative vitreoretinopathy were examined, and the following conclusions were drawn: (1) There is great variability in the phenotypic expression of the abnormal gene, such that many patients have very mild disease which can be detected with certainty only by fluorescein angiography. (2) Gene penetrance is close to 100%. (3) Progress of fundus changes and visual threat is rare after 20 years of age.

Familial exudative vitreoretinopathy was first reported by Criswick and Schepens¹ in several members of 2 families with abnormalities of the retina and vitreous which closely simulated retrolental fibroplasia, but in whom there was no history of prematurity or oxygen administration during the neonatal period. The disease was described as bilateral and slowly progressive, with a familial incidence, but of uncertain inheritance pattern. Gow and Oliver² expanded the original observations, identified autosomal dominant inheritance, and divided the clinical course into 3 stages. The fluorescein angiographic findings in familial exudative vitreoretinopathy were first described by Canny and Oliver.³ They demonstrated closure of the peripheral retinal vasculature associated with elevated, temporal fibrovascular masses, and stressed again the similarity between this entity and retrolental fibroplasia.

This report describes the fundus and fluorescein angiographic findings in 12 affected members of 3 families with autosomal dominant exudative vitreoretinopathy. In contrast to the impression given by previous reports, the disease may be asymptomatic and nonprogressive, and the clinical abnormalities difficult to identify.

Case reports

PEDIGREE 1 (Fig. 1)

Case 1 (pedigree 1, II-2). A 12-year-old Chinese female was the product of a normal gestation and delivery, and received no oxygen therapy. At 2 years of age extensive peripheral traction retinal

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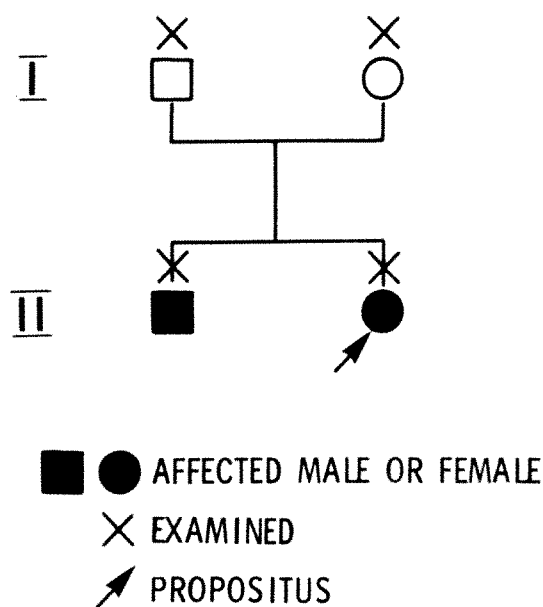


Fig. 1 Pedigree 1.

detachment was observed in the left eye. Exudates, microaneurysms, and 'abnormal vessels' were identified in the temporal periphery of the right eye, and a diagnosis of bilateral congenital retinal vascular malformations was made. The right eye remained stable until the age of 3½ years, when reduction of vision was noted. Macular exudates were associated with an angiomatous lesion and traction retinal detachment in the temporal retinal periphery. Surgery was undertaken in Australia (G. Crock), and after the procedure the retina became reattached, and vision with the right eye improved and has subsequently remained unchanged.

The patient was first seen at Moorfields Eye

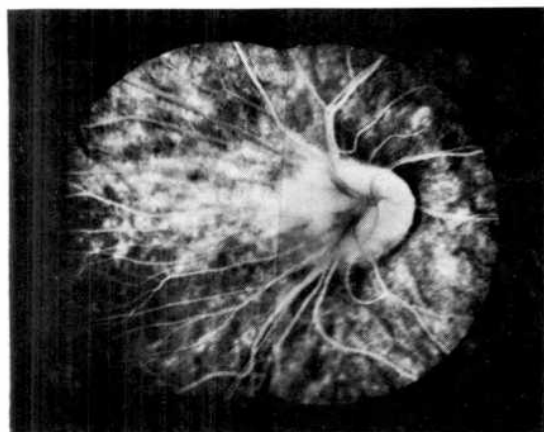


Fig. 2 Fluorescein angiogram of case 1, showing distortion of the right eye central retinal vessels and leakage into the macula area.

Hospital on 10 October 1977. Visual acuity was 6/9 (20/30) with the right eye and no light perception with the left. The left eye was soft and shrunken, with a cataract and band keratopathy preventing a view of the fundus. The right anterior segment was normal. Fundus examination of the right eye revealed temporal dragging of the posterior retina, chorioretinal scarring and pigmentation in the area of the previous retinal surgery, and retinal vessel closure anterior to the equator in all quadrants with exudates nasally. Fluorescein angiography of the right eye revealed leakage of dye from the distorted

retinal vessels in the posterior pole and at the temporal margin of the optic disc (Fig. 2). In the pre-equatorial retina the retinal vessels were increased in number, straight, and radial, and the retinal vessels ceased abruptly anterior to the equator. There was dye leakage from these vessels.

Case 2 (pedigree 1, II-1). The 17-year-old brother of case 1 was born at term and received no oxygen therapy. He was myopic, but had no other ocular symptoms and was otherwise healthy. Visual acuity was 6/5 (20/15) with the right eye (-5.25 d.sph. -3.50 d.cyl. axis 175°), and 6/5 (20/15) with the left eye (-5.00 d.sph. -2.00 d.cyl. axis 05°). The anterior segments of both eyes were normal. Fundus examination of the right eye showed moderate temporal dragging of the optic disc and macula. The peripheral vessels in all quadrants were more numerous than normal, straight, and radially orientated. The vessels ended abruptly in the pre-equatorial region with retinal nonperfusion anterior to this zone. At 10 o'clock, at the margin of vessel closure, forward vessels were associated with whitish exudates and subretinal fibrosis. The changes in the left eye were similar but less severe. Fluorescein angiography of the right eye showed an increase in the number and calibre of retinal vessels anterior to the equator; the vessels were straightened and ceased abruptly forming a scalloped border. Diffuse dye leakage occurred from the vessels posterior to the marginal closure, and prominent leakage of dye occurred from the neovascularisation in the temporal periphery (Fig. 3). The left eye

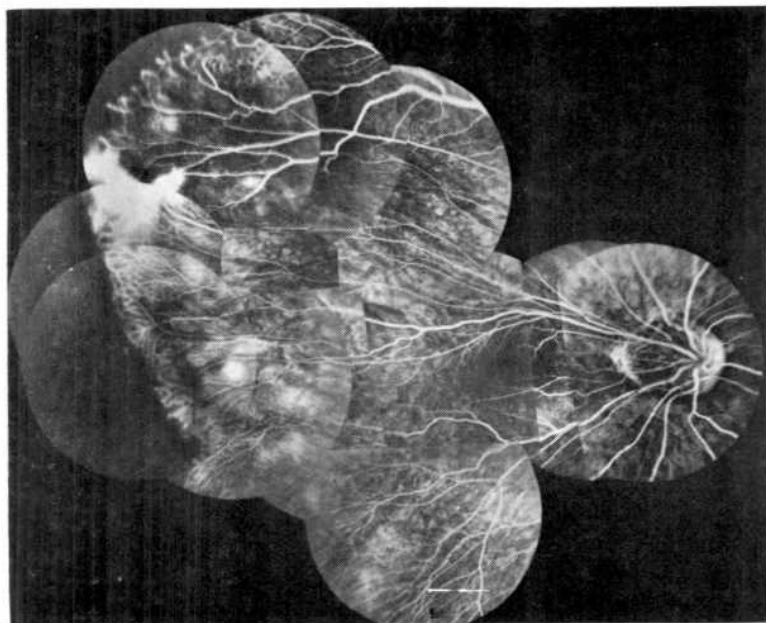


Fig. 3 Fluorescein angiogram of the right eye of case 2, showing distortion of the retinal vessels and peripheral vessel closure, with diffuse leakage from the peripheral retinal vessels and from the forward vessels.

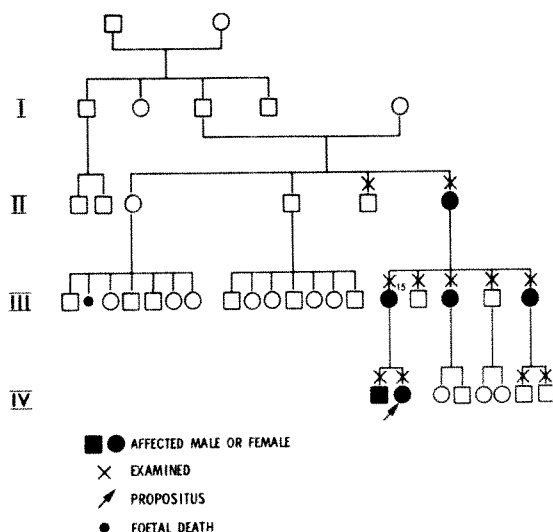


Fig. 4 Pedigree 2.

showed similar but milder changes in the peripheral retinal vasculature.

One eye of both parents was examined and no abnormalities were identified, but fluorescein angiography was not undertaken.

PEDIGREE 2 (Fig. 4)

Case 3 (pedigree 2, IV-2). A 17-year-old white female was first seen at the age of 3 years with a 3-week history of right exotropia. The patient was born at term at home and weighed 3409 g (7½ lb). She was otherwise healthy. Initial examination revealed widespread peripheral traction retinal detachment, with vitreous fibrosis in the right eye and glial tissue on the left optic disc. A congenital vascular malformation or endophthalmitis was considered a possible cause for these changes. Two and a half years later progression of the changes in the left eye was recorded; at that time vision was finger counting with the left eye, and there were dense organised vitreous bands with extensive retinal detachment. Vision was 6/60 (20/200) with the right eye, and the fundus findings were unchanged. The patient was last examined on 3 April 1978, and the visual acuity was 6/60 (20/200) with the right eye ($-200 + 1.50$ axis 100°), and no light perception with the left. The right anterior segment was normal. The right vitreous base was organised, giving rise to circumferential traction and detachment of the peripheral retina. The fibrous tissue was inserted into the optic disc with forward traction on the central retinal vessels. The left eye was soft and shrunken, and the fundus was not seen. Fluorescein angiography was not performed.

There was no family history of eye disease, but 10 other members of the family were examined; all were born at term with normal birth weight, and none was given oxygen in the neonatal period. Unless otherwise stated, none had ocular symptoms, abnormalities were limited to the fundi, and the visual acuity was 6/6 (20/20) or better with each eye.

Case 4 (pedigree 2, IV-1; 22-year-old brother of the proband). The fundi appeared normal except for an area in the left temporal periphery, where the retinal vessels appeared more numerous and straightened. Fluorescein angiography of the left eye in the temporal periphery showed an increased number of straight, parallel vessels that ended abruptly anterior to the equator in a scalloped border; fluorescein leakage occurred from a few of those vessels. Similar vascular changes were seen in the temporal retina of the right eye.

Case 5 (pedigree 2, III-15; 40-year-old mother of the proband). The posterior retinal vessels in the right eye showed mild temporal dragging (Fig. 5b). In the temporal periphery of the right eye, the vessels were straightened, and several were sheathed. In this zone the vessels were not perfused, and there were pigmentary changes and minimal yellowish, retinal exudates. The left fundus appeared normal. Fluorescein angiography of the right eye temporal periphery showed the retinal vessels to be more numerous and increased in calibre, and leakage occurred from these vessels (Fig. 5a). No perfusion occurred anterior to the equator. In the left eye, despite the normal appearance of the vessels, there was leakage into the posterior retina during angiography (Fig. 5c). The periphery showed similar vascular changes to those in the right eye, and temporally there was reduplication of the line of leaking blood vessels (Fig. 5d).

Case 6 (pedigree 2, III-17; 32-year-old maternal aunt of the proband). The posterior pole in each eye was normal. The retinal blood vessels were straightened and more numerous than normal in the temporal periphery of both eyes. Fluorescein angiography showed peripheral nonperfusion, and the vessels ended in arteriovenous anastomoses without an intervening capillary network. Central to the margin of perfused and nonperfused retina the capillaries were dilated and there was diffuse leakage of dye.

Case 7 (pedigree 2, III-19; 28-year-old aunt of the proband). The fundi of each eye were apparently normal, but fluorescein angiography showed peripheral retinal vessel closure in the temporal periphery of each eye, with dye leakage from the vessels at the border of closure.

Case 8 (pedigree 2, II-6; 60-year-old maternal grandmother of proband). Other than mild adult

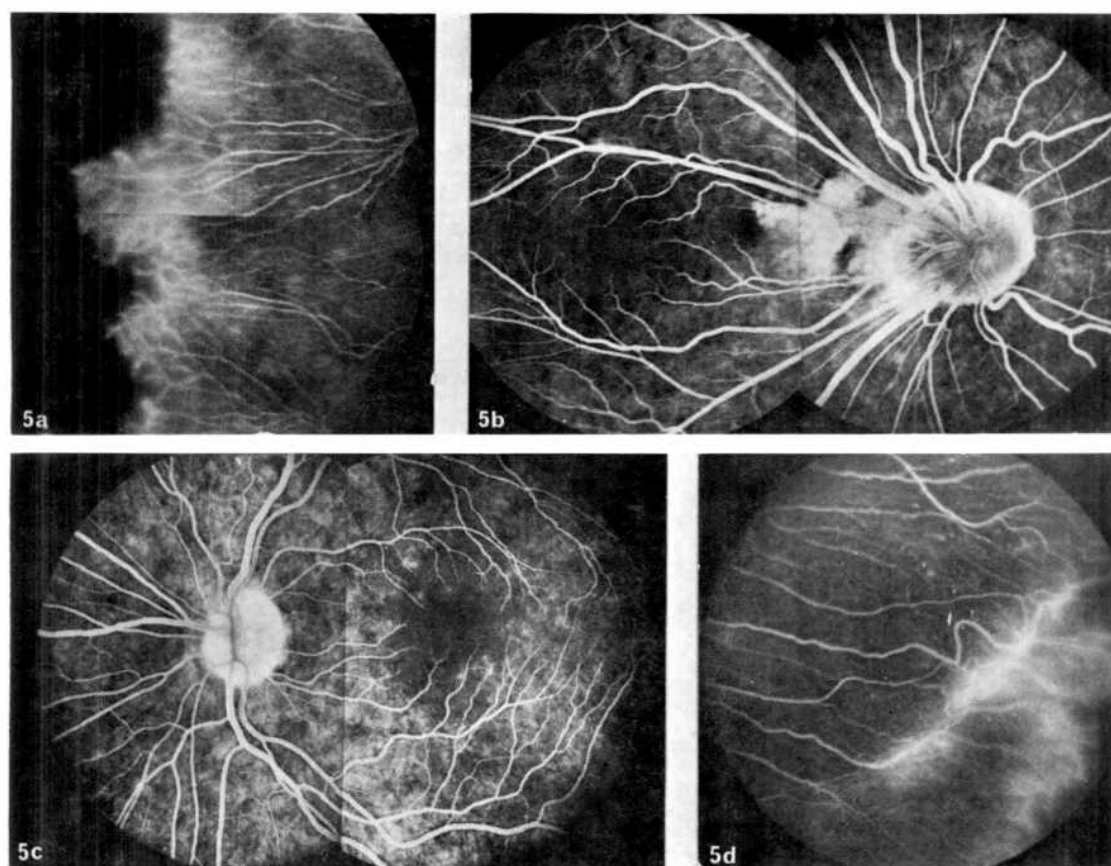


Fig. 5 Fluorescein angiogram in case 5, showing distortion of the central retinal vessels in the right eye only (5b), peripheral retinal vessel closure with leakage (5a, d) and leakage from the paramacular vessels in the left posterior pole (5c).

onset diabetes she was healthy, but had noticed recent mild blurring of vision. Visual acuity was 6/12 (20/40) in the right eye and 6/18 (20/60) in the left eye. The anterior segments showed bilateral mild nuclear sclerosis. Intraretinal haemorrhages and exudates were located in the posterior pole of each eye, and the peripheral fundus appeared normal. Fluorescein angiography revealed multifocal retinal vascular disease consistent with background diabetic maculopathy. The temporal periphery of each eye showed sharply demarcated retinal vessel nonperfusion with leakage of dye, and areas of capillary nonperfusion.

Five other members of this family were examined (IV-7, IV-8, III-16, III-18, and II-5) and fluorescein angiography undertaken on 3. They were all asymptomatic, with no history of ocular or systemic disease. Visual acuities were normal, and no ocular abnormalities were found.

PEDIGREE 3 (Fig. 6)

Case 9 (pedigree 3, III-11). A healthy 15-year-old Iranian female with decreased vision in the right eye since childhood was seen on 17 July 1978. She was born at term and was given no oxygen in the neonatal period. Visual acuity was 6/60 (20/200) with the right eye, and 6/9 (20/30) with the left eye. Except for a 30 prism dioptre right esotropia, external and anterior segment examination of each eye showed no abnormality. In the right fundus there was severe temporal dragging of the posterior retina (Fig. 7a), with circumferential traction of the temporal peripheral retina. The vitreous base was dense and organised temporally, preretinal vitreous bands were located inferiorly, 'white without pressure' was present in all quadrants, and retinal exudates were located temporally. The left eye had similar but slightly less severe changes. Several large neovascular fronds resembling 'sea-fans'

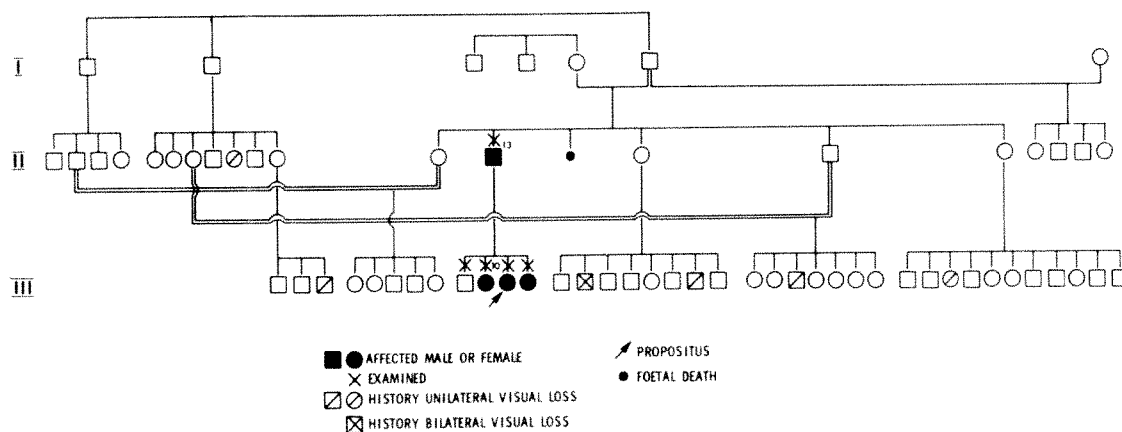


Fig. 6 *Pedigree 3.*

with feeder vessels were located in the temporal periphery.

Fluorescein angiography of the right eye showed diffuse leakage of dye in the posterior pole (Fig. 7a), and confirmed the large areas of peripheral non-perfusion. The left eye showed leakage of dye at the disc and macula, and similar peripheral non-perfusion in all quadrants. The forward neovascularisation was located at the posterior margin of the zone of peripheral closure in the temporal periphery, and leaked dye profusely (Figs. 7b, c).

Case 10 (pedigree 3, III-10; 7-year-old sister of the proband). She had poor vision since infancy but no systemic disease. Visual acuity was 2/60 (6/200) with the right eye (-3.00 d.sph. $+0.50$ d.cyl. axis 90°), and 1/60 (3/200) with the left eye (-2.50 d.sph. $+0.50$ d.cyl. axis 110°). External examination showed 'searching' nystagmus and a large variable esotropia with no fixation preference; the anterior segment was normal in each eye. The left eye showed severe temporal dragging of the posterior retina, many vitreous membranes, and a temporal fibrous mass in the peripheral retina and vitreous base which extended anteriorly to involve the ciliary body. The inner layers of the temporal retina were highly elevated by traction with several large peripheral retinal holes present. The right eye had similar but slightly milder involvement. Fluorescein angiography was not performed.

Case 11 (pedigree 3, III-12; 22-year-old sister of the propositus). The right eye was enucleated in infancy because of a possible intraocular malignancy. Correct visual acuity was 6/18 (20/60) with the left eye (-6.50 d.sph. -2.00 d.cyl. axis 165°). The left anterior segment was normal. The vitreous showed mild degeneration, snowflake vitreous opacities, and preretinal vitreous membranes inferiorly. The retina

showed moderate temporal dragging of the disc and macula, temporal retinal neovascularisation and exudates, peripheral 'white without pressure', and retinal vessel nonperfusion in all quadrants. Fluorescein angiography demonstrated the mild dragging of the posterior retinal vessels with dye leakage; there was also focal venous leakage above and nasal to the optic disc (Fig. 8a). Angiography also confirmed peripheral nonperfusion and profuse leakage from the peripheral vessels (Fig. 8b) and at the posterior pole.

Case 12 (pedigree 3, II-13; 55-year-old father of the proband). Visual acuity was 6/6 (20/20) in each eye. The anterior segments were normal. The fundi were normal except for mild retinal exudates and peripheral vessel closure in the temporal periphery of the right eye. Fluorescein angiograms were poor, but were adequate to confirm peripheral retinal vessel closure.

The 25-year-old brother of case 8 was healthy and without ocular symptoms. Ocular examinations and fluorescein angiography were normal.

Five relatives had poor vision with 1 eye and 1 with both. The cause of visual loss was unknown, and there was no opportunity to see the other family members.

Discussion

Criswick and Schepens¹ described in detail the vitreoretinal changes in 6 cases of autosomal dominant exudative vitreoretinopathy, and Gow and Oliver² described 3 clinical stages. Stage 1 showed vitreoretinal interface changes, vitreous bands and membranes, and peripheral retinal degeneration; stage 2 the occurrence of neovascularisation, retinal exudates, elevated fibrovascular

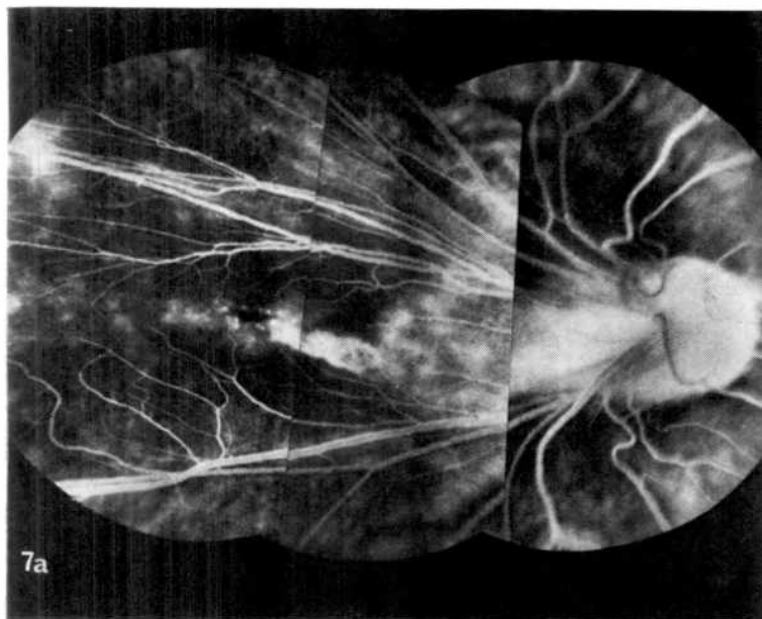
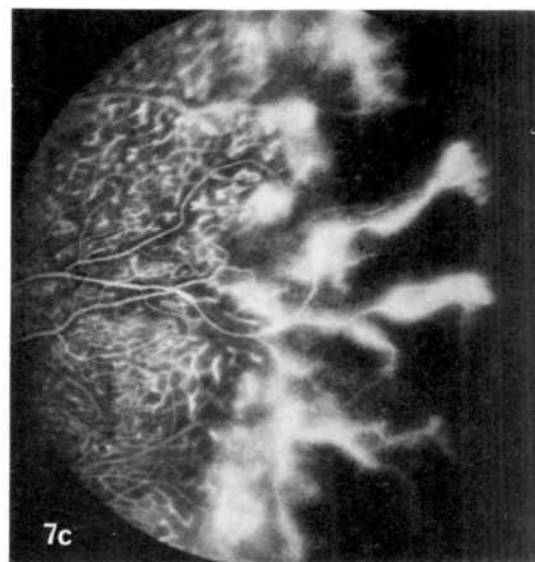
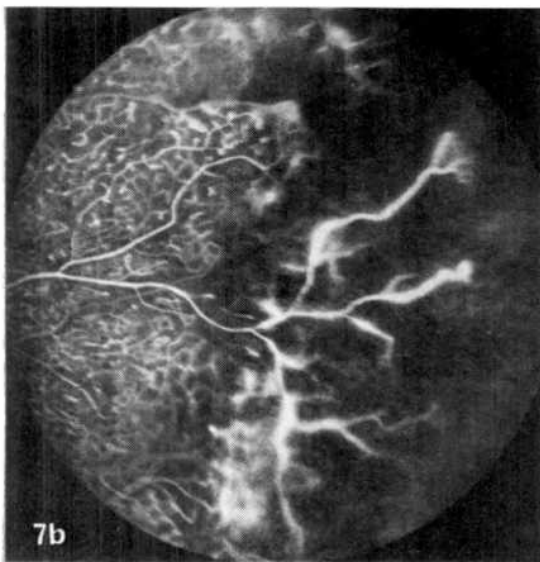


Fig. 7 Fluorescein angiogram of the right eye of case 9, showing distortion of the central retinal vessels (a). Peripheral retinal vessel closure was associated with forward new vessels (b, c).

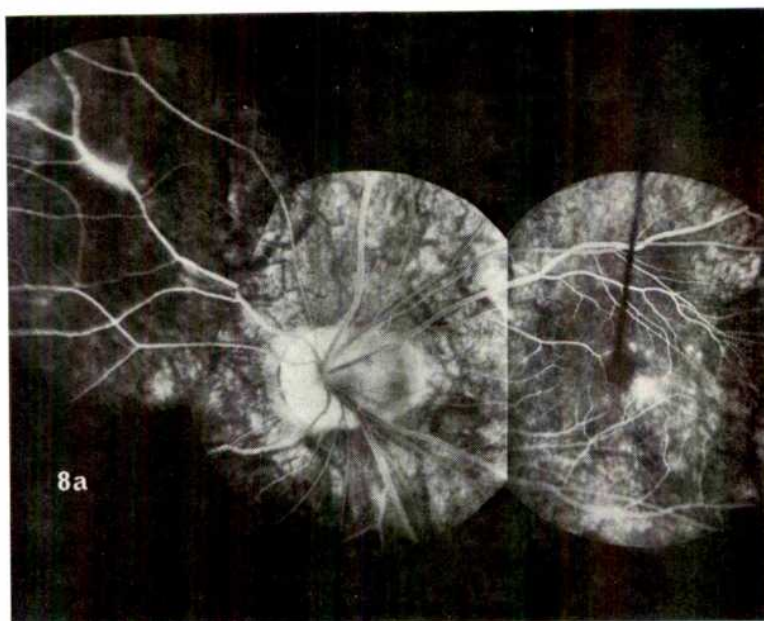


masses in the temporal periphery, localised retinal detachment, and dragging of the disc and macula; stage 3 total retinal detachment, associated with anterior segment changes comprising cataract formation, iris atrophy, neovascular glaucoma, band keratopathy, and eventual blindness.

Seven of our 12 patients had no ocular symptoms and were mildly affected by the disease (Table 1). None of these patients had 'white with pressure', 'white without pressure', or vitreous bands and

membranes, as described in stage 1 of the disease,² and only 2 of these patients had dragging of the disc and macula in one or both eyes (cases 2 and 5). In 3 of these 7 patients (cases 4, 6, and 8) the only ophthalmoscopic finding was an excess of straight vessels in the periphery, which were radial. However, all of the 7 patients had pre-equatorial nonperfusion of retinal vessels, indicating the abnormal genotype. The peripheral straight vessels and peripheral nonperfusion, which were difficult to detect ophthal-

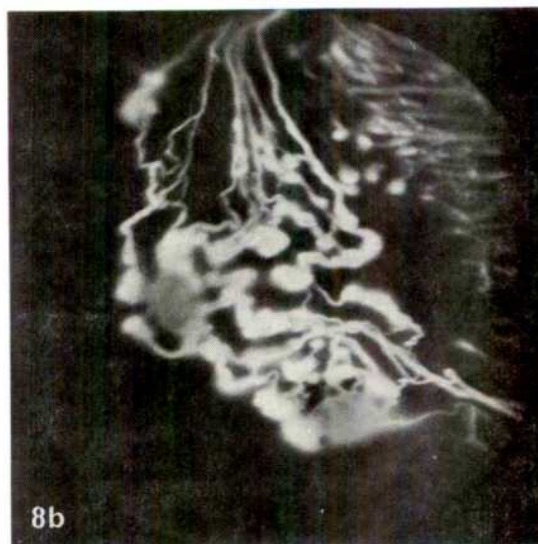
Fig. 8 Fluorescein angiogram of case 11, showing distortion of the central retinal vessels with leakage and dye in the macular region and from a nasal retinal vein (a). Peripheral nonperfusion was associated with retinal telangiectasis (b).



moscopically, were easily demonstrated by fluorescein angiography. Abnormality of the vitreous, as described in the first reported cases, was not a prominent feature in many of our cases and does not appear to be essential in making the diagnosis. We conclude that, if the stated criteria of Gow and Oliver² had been adhered to, some of these cases might not have been identified.

Understandably, most emphasis has been placed on the peripheral retinal vascular changes. The pattern of peripheral closure and forward proliferation of new vessels has been well described,^{3,4} but the retinal vessel abnormalities appear to be more widespread. In several cases fluorescein leakage occurred over a wide band of postequatorial retina, and in 3 cases there was leakage from the macular capillaries even in the absence of gross traction (Fig. 5c).

Progressive traction causing retinal detachment and vitreous haemorrhage from forward retinal blood vessels may be construed as the major threat to vision in these patients. Criswick and Schepens¹ judged the chances of complete arrest of the condition to be small, and Gow and Oliver² also emphasised the progressive nature of the condition. Photocoagulation or cryotherapy have been recommended if progress is identified.^{1,2} In each case it was implied that therapy should be directed to the proliferating peripheral new vessel complexes. If the object of this treatment was to reduce the incidence of vitreous haemorrhage, there is little evidence to justify this. Vitreous haemorrhage has



been recorded in only 1 patient.¹ This patient had a horseshoe tear, and no evidence was presented to indicate that the forward vessels were the source of haemorrhage.

Contrary to the impression given by these earlier papers,^{1,2} but in accord with the reservations of Gitter and co-workers,⁴ our findings suggest that the disease does not necessarily progress relentlessly during life, and in this respect differs from the recorded behaviour of Wagner's hyaloretinopathy.⁵ In our pedigrees, and in those already published, no

Table 1 Ocular involvement in affected members of 3 families with autosomal dominant vitreoretinopathy

	Age	Sex	Vision	Symptoms	Dragged disc/ macula	Peripheral exudates/ fibrosis	Peripheral non- perfusion	Neo- vasculari- sation	Traction detachment	Vitreous bands/ membranes
<i>Pedigree 1</i>										
Case 1 (II-2)	12	F	OD 6/9 (20/30) OS NLP	Yes	+++ No fundus view	+	Yes	No	-	-
Case 2 (II-1)	17	M	OD 6/5 (20/15) OS 6/5 (20/15)	No	++ +	+	Yes Yes	Yes No	- -	- -
<i>Pedigree 2</i>										
Case 3 (IV-2)	17	F	OD 6/60 (20/200) OS NLP	Yes	+++ No fundus view	+++	Yes	No	+++	+++
Case 4 (IV-1)	22	M	OD 6/5 (20/15) OS 6/6 (20/20)	No	- -	-	Yes Yes	No No	- -	- -
Case 5 (III-15)	40	F	OD 6/6 (20/20) OS 6/6 (20/20)	No	+	+	Yes Yes	No No	- -	- -
Case 6 (III-17)	32	F	OD 6/6 (20/20) OS 6/5 (20/15)	No	- -	-	Yes Yes	No No	- -	- -
Case 7 (III-19)	28	F	OD 6/5 (20/15) OS 6/5 (20/15)	No	- -	-	Yes Yes	No No	- -	- -
Case 8 (II-6)	60	F	OD 6/12 (20/40)* OS 6/18 (20/60)	No	- -	-	Yes Yes	No No	- -	- -
<i>Pedigree 3</i>										
Case 9 (III-11)	15	F	OD 6/60 (20/200) OS 6/9 (20/30)	Yes	+++ ++	+++ ++	Yes Yes	No Yes	+++ ++	++ ++
Case 10 (III-10)	7	F	OD 2/60 (6/200) OS 1/60 (3/200)	Yes	+++ +++	+++ +++	Not determined	No No	++ +++	++ +++
Case 11 (III-12)	22	F	OD Prosthesis OS 6/18 (20/60)	Yes	++	++	Yes	Yes	-	+
Case 12 (II-13)	55	M	OD 6/6 (20/20) OS 6/6 (20/20)	No	- -	+	+	No No	- -	- -

+++ = Severe. ++ = Moderate. + = Mild. - = Not present.

*Decreased vision caused by diabetic maculopathy.

member has been reported as suffering from loss of vision after the age of 20 years, and the disease was not obviously more advanced in older than in younger patients with the abnormal gene. It is perhaps significant that those workers who undertook treatment as a result of documented progression did so in patients under the age of 18 years. However, even in the young progression is not inevitable. Case 3 was remarkable in that there was traction detachment of the whole pre-equatorial retina of the right eye at the age of 2½ years which did not progress during the following 14 years. The only case in this series who was treated had retinal detachment with loss of central vision (case 1), and vision has remained good during the subsequent 8½ years.

If our observations are representative of the disease as a whole, and our interpretation of pre-

vious reports is correct, doubt is cast on the need for any type of prophylactic measure, even in the presence of marked abnormality. It is possible that treatment should be limited to those patients in whom there is visual loss. Furthermore, the lack of progression indicates that no visual threat to the patient is implied by making the diagnosis in an adult during family survey.

Gow and Oliver³ described an autosomal dominant pattern of inheritance with reduced penetrance, because family members with the abnormal gene were found to have normal fundi (patients V-29 and V-30); we assume fluorescein angiography was not performed in these cases. In our second pedigree there were 3 affected members out of 6 relatives at 50% risk of inheriting the abnormal gene, which suggests that the penetrance is close to 100%, and the apparent reduction in penetrance is due to

variable expressivity. Because of possible mild involvement we doubt whether an eye can be considered normal without careful indirect ophthalmoscopy, 3-mirror contact lens examination, and fluorescein angiography. It is likely that the phenotypic expression of the abnormal gene would have been detected in one parent of the propositus in the 2 families studied by Criswick and Schepens¹ and in the other eye of the reported unilateral cases² if fluorescein angiography had been performed. One eye of each parent in pedigree 1 was dilated and found to be normal, but careful 3-mirror contact lens examination and fluorescein angiography were not done.

The variable expressivity of autosomal dominant exudative vitreoretinopathy has further implications for the identification of heritable disease and genetic counselling. A negative family history of poor vision does not exclude the diagnosis of this genetically determined disease. Furthermore, individuals at risk of having the abnormal gene and seeking genetic advice require a careful examination of the retinal periphery and fluorescein angiography before accurate genetic counselling can be given. The variable expressivity also casts doubt on the diagnosis of retrolental fibroplasia in the absence of prematurity⁶ and neonatal administration of oxygen, unless other members of the family have been fully assessed.

The pathogenesis of autosomal dominant exudative vitreoretinopathy is unknown. The sharply demarcated zone of peripheral retinal blood vessel closure and the pattern of arteriovenous anastomoses are remarkably similar to retrolental fibroplasia.⁷⁻⁹ The 2 conditions appear to be morphologically indistinguishable, and it is possible that there

are similarities in the pathological mechanisms between them. Observations of the fundus of patients at risk of inheriting the abnormal gene during the neonatal period may help to explain the morphology of the lesion, and the finding that the visual prognosis appears to be determined in the first 2 decades of life.

Dr Richard R. Ober was supported by the Francis and Renee Hock Fellowship. We thank Miss J. Bramley and Mrs E. Barrera for secretarial assistance and are grateful to Professor G. Crock and Mr A. S. M. Lim for allowing us to publish case 1.

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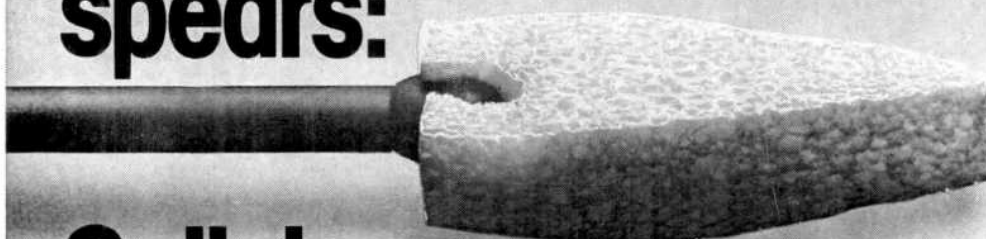
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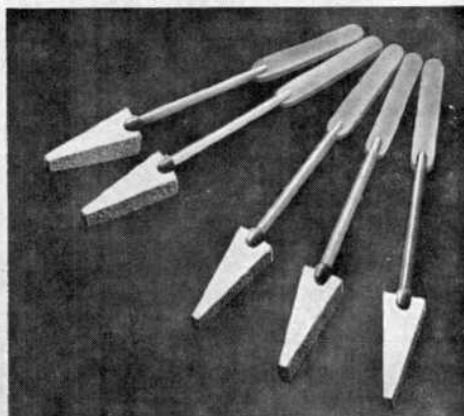


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Retinal detachment in median cleft-face syndrome

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SUMMARY A 7-year-old boy had an unusual association of median cleft-face syndrome, a characteristic physiognomy, unilateral retinal dysplasia, and bilateral retinal detachment. Despite surgical treatment to both eyes he became blind. The hereditary pattern operating in this complex disorder was found to be consistent with an autosomal dominant trait.

The occurrence of retinal detachment in median facial defects has been described in syndromes which differ both in morphology and in the mode of inheritance. These anomalies appear from the literature to be causally and pathogenetically related, through a concomitant developmental defect.

The present report concerns a family pedigree in which 1 boy presented with a median cleft-face syndrome¹ associated with primary retinal dysplasia in 1 eye, later developing bilateral blinding retinal detachments.

Case report

The initial contact with the proband (Fig. 1, II-6) was in 1972, when at the age of 5 he was brought to hospital urgently with a history of loss of vision in his good right eye. His medical history revealed that shortly after birth he had difficulty in breathing and was found to suffer from median cleft nose, median cleft upper lip, and complete cleft palate. Later he underwent a surgical correction for his midfacial defects. He had had a normal gestation and delivery, had been a full-term child and did not require oxygen therapy during infancy. His mother had not been exposed to teratogenic factors during the gestational period. Three years before the onset of the visual symptoms he underwent an eye examination and was found to have a high myopia (-14.0 D). The corrected visual acuity in the right eye was 20/80. The left eye was found to have no potentially useful vision and was diagnosed as having retinal dysplasia.

The eye examination when he was in hospital disclosed a visual acuity of 1/20 in the right eye and

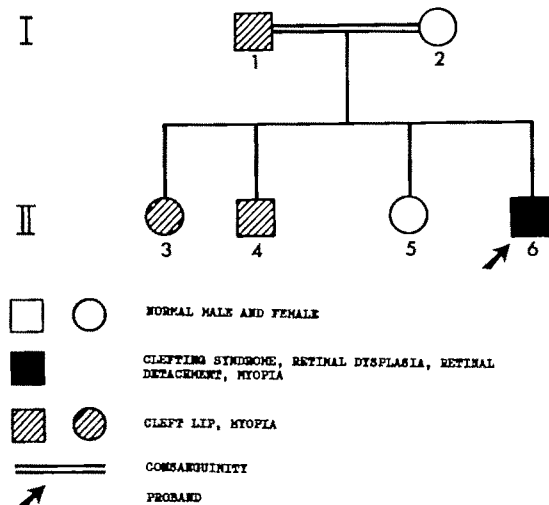


Fig. 1 Family pedigree

only hand movements in the left. The anterior segments appeared normal except for a slight left enophthalmos. The intraocular pressure was 10 mmHg. There was normal movement of the globes in all positions of gaze. Sluggish pupillary reflexes were obtained, but the pupils dilated reasonably well. The lenses were clear.

Ophthalmoscopic examination showed a right bullous rhegmatogenous retinal detachment, with multiple retinal tears and holes, extending from the periphery to the optic disc in all the quadrants, partially sparing the macula. Translucent strands and vitreal liquefaction gave the impression of an optically empty vitreous cavity. In the left fundus a proliferative whitish fibrous tissue emanating from the optic disc was found. This patchy proliferative tissue, extending to the temporal upper periphery, was surrounded by scattered pigmentary clumps

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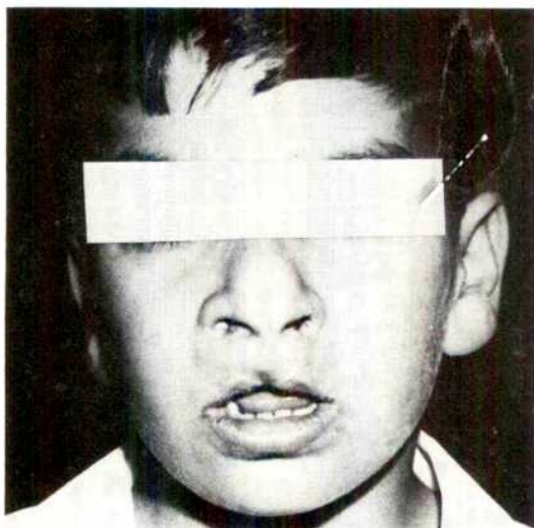


Fig. 2 Frontal view of the proband's face. Note the corrected midfacial defects and the broad nasal bridge

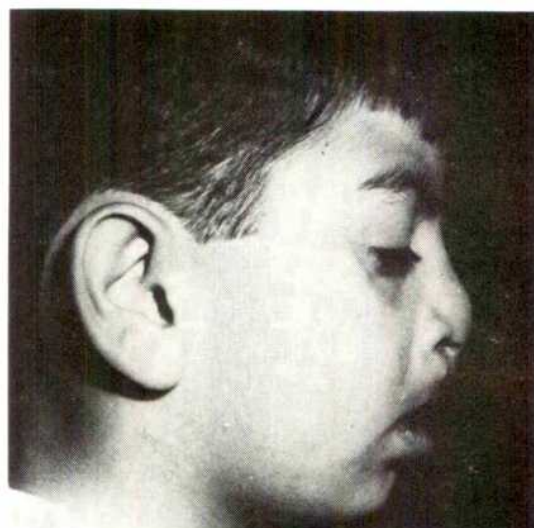


Fig. 3 The characteristic physiognomy with the midfacial flattening

and ended in a veil-like retinal fold. The lower retinal part was completely detached, with massive periretinal proliferation.

Repair of the right detached retina was attempted with a wide scleral trapdoor, diathermy in the bed, a 12 mm silicone tire, an encircling band, drainage of subretinal fluid, and intravitreal injection. The retina was flat for 3 days after operation, but became detached again soon afterwards, developing periretinal membranes with funnel-shaped fixed folds. A second attempt at repair was unsuccessful. After the failure in the right eye surgical repair of the left eye was performed, but despite the intervention this eye too remained inoperably blind.

As the retinal findings were found to be associated with median facial defects, a complete medical examination was carried out. Physically the child was in good health. Significant findings were confined to the face. The frontal view revealed hypertelorism, with interpupillary distances falling only slightly above the upper limits of the normal. Only a rudimentary remaining defect of his upper lip and nose was noted (Fig. 2). A characteristic maxillary hypoplasia with the nasal defect gave the appearance of a flattened mid-face (Fig. 3). The remainder of the physical examinations of the skeleton and chest, routine laboratory examinations, and a chromosomal analysis were normal. The child's mentality was considered to be borderline.

The family history revealed that the parents were consanguineously related, being first cousins. The father (Fig. 1 I-1) had a surgically corrected cleft lip and was myopic (-5.0 D). Neither parent had

any other special diseases. They had 2 other mildly myopic children born with cleft lips, later surgically corrected (Fig. 1 II-3, II-4). Another physically healthy daughter presented no median face defects and was found to be emmetrope (Fig. 1 II-5). An inquiry among the family members of the parents revealed that no others had showed similar findings.

Discussion

Retinal detachment in connection with malformations of the face has been found frequently enough to establish clearly that we are dealing with syndromes rather than fortuitous associations.²⁻⁴ The literature contains a confusing multitude of variant syndromes in which vitreoretinal degeneration and median cleft-face defects are associated with a variety of additional systemic anomalies.⁵⁻⁷ The clinical variability of these defects and their familial aggregations give considerable support to the assumption that genetic factors play an important role in their aetiology.

In our case the median facial defects and the characteristic physiognomy consisting of maxillary hypoplasia, the broad nasal bridge, and midfacial flattening was associated with unilateral retinal dysplasia, a joint occurrence which is certainly rare. No reports of an association between retinal dysplasia and cleft defects have been found except complex disorders such as Meckel syndrome⁸ or chromosomal aberrations.⁹ The severe vitreous changes in the form of liquefaction and preretinal membrane formation in the patient's highly myopic

eyes were complicated by bilateral retinal detachments. Surgical repair had been attempted, but despite all treatments both eyes became inoperably blind, confirming previous similar impressions.¹⁰ These failures after conventional encircling techniques suggested the possibility of poor retinal tissue response to surgery, particularly when it was not followed by vitrectomy.¹¹

The midfacial defects found in the father and the patient's sibs were helpful in tracing the path of the mutant gene in the pedigree. The most likely mode of inheritance in this family seemed to follow autosomal dominant transmission. The pedigree shows that a minimally affected parent may have a severely affected offspring and that the symptoms appeared in members of 2 successive generations, with both sexes affected. Interestingly a consanguineous mating between the affected father and his phenotypically normal cousin—the mother—took place. Three classes of offsprings were expected among the progeny of this union, namely, homozygous normal, heterozygous affected, and homozygous affected, in a distribution of 1:2:1 respectively. This prediction seems to have been realised in that 1 child appears to be unaffected (II-5), 2 others (II-3, II-4) display lesions of mild severity similar to that of their father's (I-1) and 1 is affected much more severely (II-6), suggesting homozygosity for the gene. If we reject such a hypothesis, it is difficult to conceive any simple explanation for the distribution of the defects in this pedigree.

All the previously described dominant syndromes of this kind, like Wagner syndrome,¹² Stickler syndrome,⁵ Cervenka syndrome,³ and others present identical vitreoretinal findings, the difference in the clinical appearance depending merely on the variability of the associated systemic defects. Their similar clinical manifestations and inheritance seem to confirm the validity of the concept that all these

syndromes are fundamentally related diseases representing deviating manifestations of the same kind of mutant gene.¹³

As the nature of these anomalies remains in part obscure, it is evident that further understanding of these complex disorders requires the investigation of additional cases.

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Sector retinitis pigmentosa in juvenile nephronophthisis

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SUMMARY In a patient with juvenile nephronophthisis, sector retinitis pigmentosa was found as an extrarenal manifestation, establishing a hitherto undescribed variety of retinal degeneration occurring in this disorder. The retinal function in this case was identical with that in the classic type of sector retinitis pigmentosa, namely, subnormal ERG amplitudes but normal cone and rod implicit times. The range of the retinal findings and their autosomal recessive transmission are discussed. Paucity of information makes it difficult to elucidate the basic genetic defect operating in this condition.

Juvenile nephronophthisis (Fanconi *et al.*, 1951) and medullary cystic disease (Smith and Graham, 1945) are hereditary conditions characterised clinically by failure to thrive, anaemia, hyposthenuria, and salt craving, followed by early uraemia. The consensus of most observers is that these diseases are identical, and owing to their clinical and pathological similarities they have been grouped together (Mongeau and Worthen, 1967).

The presence of extrarenal manifestations in juvenile nephronophthisis is obvious (Mainzer *et al.*, 1970; Boichis *et al.*, 1973), and the most frequent allied condition is tapeto-retinal degeneration (Senior *et al.*, 1961). There is ample evidence of such an association in familial cases, and it appears to be due to a pleiotropic effect of the gene involved and not a coincidence of symptoms. A common genetic background for the renal and retinal disorders has been postulated and autosomal recessive inheritance invoked.

We report here a new case of juvenile nephronophthisis which involved a type of retinal degeneration not yet reported in connection with this complex renal disorder.

Case report

Our interest in this 18-year-old woman was stimulated during routine investigation for possible ocular abnormalities in patients on chronic haemo-

dialysis. The onset of her renal disorder began 7 years earlier with a normocytic anaemia. Polydipsia and polyuria were observed clinically, and tests of kidney function showed impaired urinary concentrating abilities. Later a high blood urea and serum creatinine were found. A drip intravenous pyelogram showed poor excretion, though there was no anatomical defect. As kidney function deteriorated, a percutaneous kidney biopsy was performed. Findings included scattered medullary cysts and extensive glomerular destruction with interstitial fibrosis and hyalinisation. These histological findings confirmed the clinical suspicion of juvenile nephronophthisis, and the patient was signed up for a haemodialysis programme and future kidney transplant.

She had no visual complaints and was unaware of any ocular disease. An audiogram indicated normal hearing function. She had normal visual acuity and the anterior segments were within normal limits. Ophthalmoscopy disclosed normal optic discs and free maculae. The central parts of the retinal vessels were of normal calibre. Symmetrical bone-corporuscle-like pigment clumps were found in the lower temporal quadrants of both eyes (Fig. 1). These abnormal areas of pigmentation were situated in the region of the equator and anterior to it. The retinal vessels were narrowed and disappeared towards the periphery. The pigment epithelium was atrophied. Colour vision was normal, but in the visual fields large scotomas were found bilaterally in the upper nasal quadrant, corresponding to the retinal lesions.

The retinal function profile, investigated by means of electroretinography, showed subnormal ampli-

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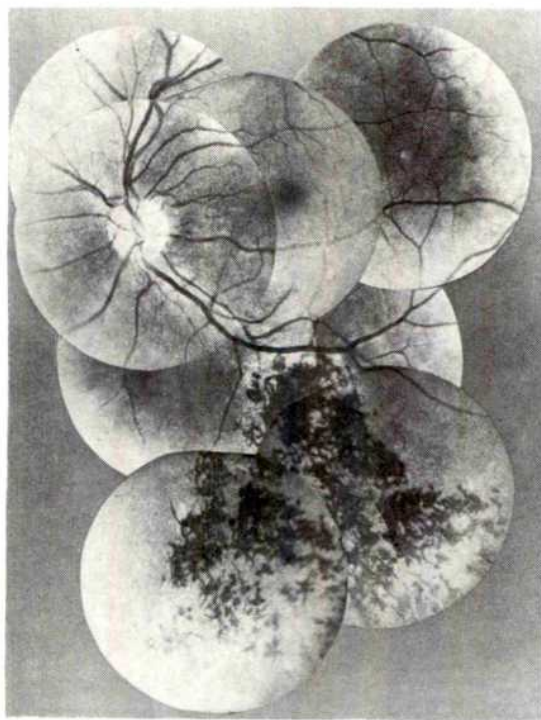


Fig. 1 The fundus of the proband. Note the sectorial distribution of the pigmentary clumps

tudes during the whole process of dark adaptation. There was some increase of the positive ERG amplitudes as a function of stimulus intensity at the steady state of dark adaptation, but they were below the normal values (Fig. 2). Despite the incomplete recovery of the ERG amplitudes, the peak latencies of the positive wave were normal for both photopic and scotopic components. The ERG amplitude response was lower than could be predicted by the ophthalmoscopic retinal appearance.

The family pedigree (Fig. 3) disclosed that the proband had a healthy younger brother and another brother who died at 6 years of age following end-stage uraemia. Neither ocular examination nor necropsy was carried out in this case. The parents were first cousins and had not had any significant illnesses. The pregnancies were without problems, and there was no exposure to teratogenic agents. According to the parents the birth weights of the proband and of the deceased child were lower than that of the healthy sib. The parents did not mention any special difficulties in the birth of these children. Inquiry among other family members affirmed that no one showed any symptoms of this syndrome. The parents themselves had normal renal and retinal functions.

Discussion

The concurrence of the renal and the retinal disorders in our case, known to exist as separate conditions, does recall some observations made in previous cases. Various retinal degenerations have been reported to be associated with juvenile nephronophthisis, and they apparently represent different

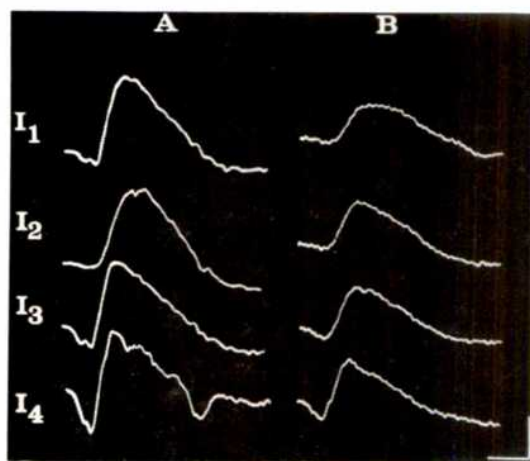


Fig. 2 The electroretinogram of our patient (B) compared with a normal case (A). These electrical responses, after full dark adaptation, were elicited with different intensities (I1–I4). Note the reduced positive amplitude but normal photopic and scotopic implicit times in the index case. Calibration 200 μ V, 40 ms

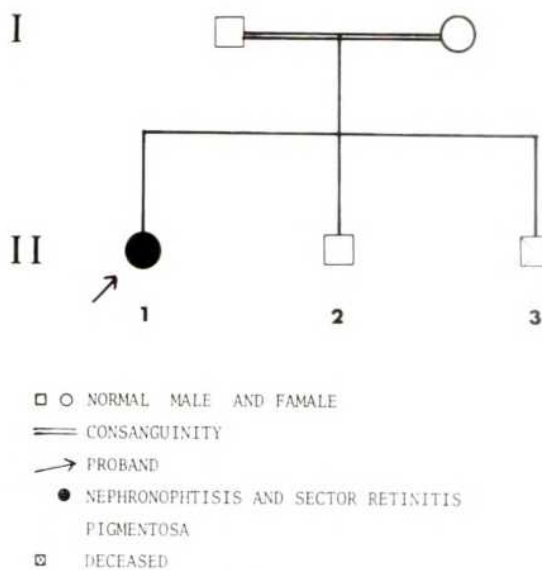


Fig. 3 Family pedigree

forms of the same disease rather than distinct entities. Among the retinal manifestations of this renal disorder congenital Leber amaurosis (Hussels, 1971; Godel *et al.*, 1978), retinitis pigmentosa (Senior *et al.*, 1961), and central retinitis pigmentosa (Price and Pratt-Johnson, 1970) were described. Our case illustrated a new variety of retinal disease appearing in association with the renal lesions. While such an association may be considered merely fortuitous, evidence has been reported of such relationships between retinitis pigmentosa or its variants and this renal disorder.

There is no argument over the familial nature of this disorder, and the consistency of reported cases leaves little doubt that it is genetically determined. The fact that different retinal disorders occur in different kindreds with juvenile nephronophthisis suggests that a biological mechanism keeps the genes for the syndrome together.

The pedigree of our family supports the interpretation that this disease is due to a recessive gene. Since both parents show no clinical evidence of the disease and they themselves are first cousins, it would seem logical to invoke a recessive pattern of transmission here. Furthermore, affected members of both sexes (the proband and the deceased child) had a normal sib, and there is no known history of other relatives of the parents being so affected.

While there seems little doubt that this genetic syndrome is an autosomal recessive trait, the wide range of retinal anomalies reported suggests there is some variability in the expression of the genetic defect. One might argue that our proband, who presents the typical picture of juvenile nephronophthisis, is affected by an unusual retinal condition which alters the typical expression of the syndrome. This unusual retinal condition, diagnosed by ophthalmoscopy, appeared in the form of typical sector retinitis pigmentosa. Its retinal functional characterisation by electroretinograms showed that the defective scotopic activity was due to a retinal involvement larger than that which could be seen by simple funduscopy. This finding confirms previous reports (Krill *et al.*, 1970) showing that the morphological retinal defect is more widespread than the ophthalmoscopic appearance would suggest.

As regards the temporal aspects of the electroretinograms, normal cone and rod implicit times were found in our case to be in accordance with previously reported findings in this retinal condition (Berson and Howard, 1971).

Although several pedigrees have been reported, no parents have yet been shown convincingly to have renal or retinal changes. In some cases the discovery of a urinary concentrating defect (Pedreira *et al.*, 1968) or electroretinographic changes (Polak

et al., 1977) in one of the parents or siblings of affected offsprings has raised the question of a heterozygous state. No such signs of heterozygosity were found in our family.

Unfortunately our family provided no additional information on the nature of the basic genetic defect in this disease. There are some suggestions that the renal involvement is not only genetically determined but might be due to an inborn error of metabolism (Schimke, 1969). Present laboratory methods, however, are not sensitive enough to isolate the enzyme abnormalities.

Since the retinal findings in juvenile nephronophthisis take various forms and occur more frequently than has been assumed, careful ophthalmoscopic examination of every such patient would seem to be necessary.

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A patterned macular dystrophy with yellow plaques and atrophic changes

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SUMMARY Three middle-aged male patients are described with a peculiar patterned dystrophy of the macula. The basic lesions are discrete yellow plaques typically confined to the macular area and radiating from the fovea. They appear to be located at the level of the retinal pigment epithelium (RPE). With the passage of time some of the yellow plaques altered in extent and configuration, and atrophic changes appeared or extended. Visual acuity and electrophysiological tests are either normal or only moderately affected. The lesions appear to be distinct from the patterned dystrophies of the retina already described and from other conditions characterised by yellow or white deposits at the level of the RPE.

Several varieties of patterned dystrophy of the retinal pigment epithelium (RPE) have been described. They include Sjögren's reticular dystrophy of the retinal pigment epithelium,^{1,2} macroreticular dystrophy of the retinal pigment epithelium,³ and butterfly-shaped pigment dystrophy of the fovea.⁴ The lesions are inherited, bilateral, and symmetrical and occur at the level of the RPE. The patterned dystrophies of the RPE do not significantly alter visual functions, and psychophysical and electrophysiological tests are generally only slightly affected.

Recently macroreticular, butterfly-shaped, and possibly reticular dystrophy of the RPE have all been observed in one family, suggesting a link between the patterned dystrophies of the RPE.⁵ This report describes 3 patients with an unusual bilateral and symmetrical dystrophy of the macular region characterised by discrete, yellow, plaque-like lesions at the level of the RPE and central atrophic changes of the outer retina.

Case reports

PATIENT 1

A 57-year-old male was seen by one of us (D.A.) in February, 1974 with a 6-month history of deterioration of vision in his left eye. He noticed that the 'middle of the word disappeared' when reading

with his left eye. The patient had no history of previous eye disease or defective night vision, and no member of his family had any significant eye complaints.

On examination the best corrected visual acuity was 6/6 right eye and 6/18 left eye. The anterior segments of the eyes were normal apart from an unusual vascular malformation of the right iris, which was considered an incidental finding. Each fundus showed oval or oblong, yellow-white plaques arranged about the macula in a spoke-like configuration often impinging on the fovea (Fig. 1).

The lesions were relatively discrete and associated only with subtle proliferative and atrophic changes in the nearby RPE. Fundus biomicroscopy and stereoscopic photography indicated that the plaque-like lesions were slightly raised and located at the level of the RPE. There was no evidence of inflammation of the retina, choroid, or posterior vitreous.

The left eye showed multiple, small, discrete, white deposits within a central circular zone of pigment epithelial atrophy at the fovea. Several yellow-white plaques radiated from the central atrophic hub (Fig. 2). Fluorescein angiography of both posterior fundi (Figs. 3, 4) showed clearly defined areas of hyperfluorescence consistent with an abnormality of the RPE. The fluorescent defects were more widespread than would have been predicted from ophthalmoscopy. The discrete yellow-white plaques remained hypofluorescent for the most part throughout angiography, and, although some staining of the adjacent RPE was

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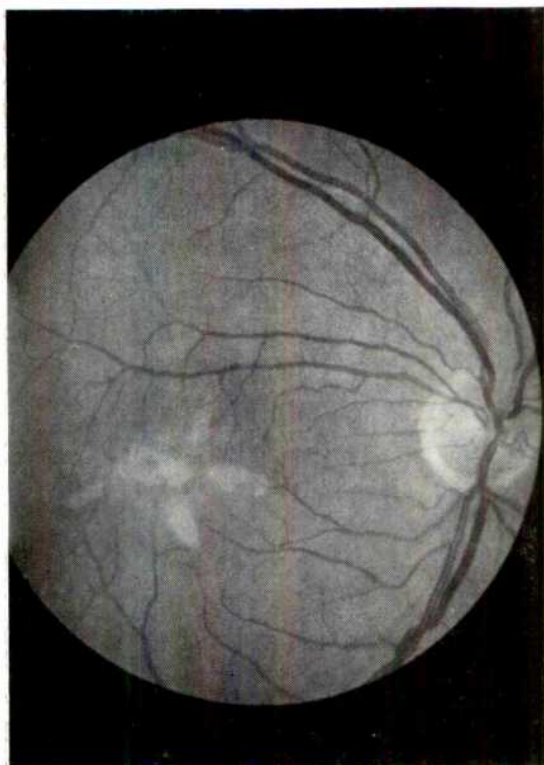


Fig. 1 Photograph right fundus, patient 1 (1974). Discrete plaques measuring one-third to one-half disc diameter (DD) in size radiate from the foveal region.



Fig. 2 Photography left fundus, patient 1 (1974). Plaque-like lesions are arranged about the central circular area of pigment epithelial atrophy.

obvious in the late phases of angiography, there was no evidence of dye extravasation beyond the retinal pigment epithelial barrier into the outer retina.

Punctate hyperfluorescent defects were also noted beyond the macula in each eye, indicating a more widespread involvement of the RPE.

Static and kinetic perimetry (Tübinger) revealed a relative central scotoma in the right eye and a small absolute central scotoma in the left eye. The Farnsworth-Munsell 100 hue test revealed no specific colour vision abnormality, but the electro-oculogram (EOG) was subnormal in each eye, i.e., 1.5 right and left (lower limit of normal is 1.8 for laboratory conditions). The photopic and scotopic electroretinographic responses were within normal limits. A genetic survey did not reveal any similar lesions in members of the family examined.

The fundus lesions were observed over a period of almost 4 years, during which time most of the oblong, yellow-white plaques either faded, diminished in size, or disappeared.

In one or two areas the plaques extended or

increased in size and in 1 eye several fresh, white deposits occurred within and superior to the macula (Fig. 5, arrows). The new plaques were morphologically and angiographically identical to those initially noted 4 years previously. An atrophic circular lesion of the RPE developed at the right fovea and intensified and increased in size at the left fovea (Fig. 6). Fluorescein angiography showed a slight increase in the area of defective pigment epithelium at the macula, but there was no evidence of fluid accumulation either in the subpigment epithelial or subretinal spaces. Visual fields showed some intensification of the central and paracentral scotomata in each eye, though visual acuity remained 6/6 right and 6/18 left. Electrophysiological tests revealed no progression of the functional abnormalities.

PATIENT 2

A 41-year-old male was referred to one of us (D.A.) in February 1975 complaining of slight deterioration of vision in both eyes and in particular the left eye. The patient had attended the Eye Clinic in 1966

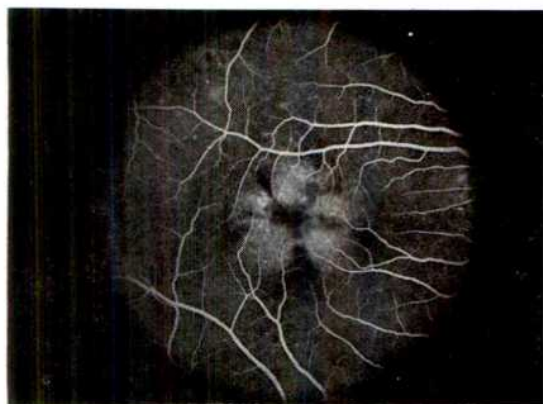


Fig. 3 Venous phase fluorescein angiogram of fundus shown Fig. 1. There is a discrete abnormality of the retinal pigment epithelium involving the macula. The plaque-like lesions are mostly hypofluorescent.

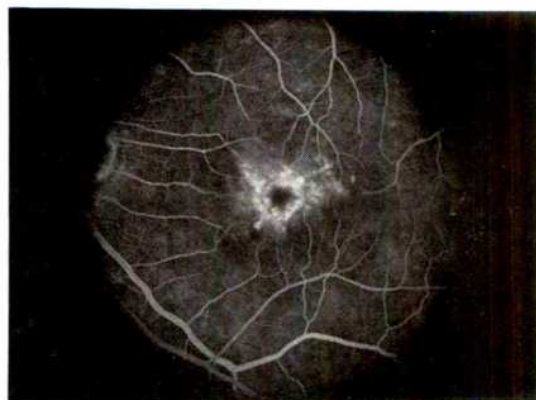


Fig. 4 Late phase fluorescein angiogram of fundus shown Fig. 2. The macula shows a mottled hyperfluorescence with some staining of the retinal pigment epithelial layer.



Fig. 5 Photograph right fundus patient 1 (1977). Some of the plaque-like lesions have faded, others have extended. Fresh lesions have occurred above the macula (arrows).



Fig. 6 Photograph left fundus, patient 1 (1977). The plaque-like lesions have faded and the central circular atrophic area has increased in size.

with recurrent attacks of bilateral episcleritis, and visual acuity at that time was recorded as 6/5 right and left. The patient gave no history of defective night vision and was in good general health.

On examination the best corrected visual acuity was 6/9 right and 6/12 left. Static and kinetic Tübinger visual fields showed no abnormality, and colour vision was normal by the Farnsworth-Munsell 100 hue test. The EOG was normal in the right eye (2.0) but significantly reduced in the left eye (1.17). Photopic and scotopic electroretinographic recordings were within normal limits for each eye.

Both fundi showed circular or oblong, yellow-white plaques at the macula (Figs. 7, 8) situated at the level of the RPE. There were scattered areas of retinal pigment epithelial atrophy and proliferation

at and near some of the plaques and a well-defined, discrete circular zone of pigment epithelial atrophy at each fovea. Fluorescein angiography confirmed the presence of a retinal pigment epithelial abnormality at and surrounding each fovea. The dense yellow-white plaques and foci of pigment accumulation were hypofluorescent, and areas of pigment epithelial atrophy were hyperfluorescent (Figs. 9, 10).

Over a period of 2½ years the yellow-white lesions became less distinct and the central circular zone of retinal pigment epithelial atrophy became more marked. Fluorescein angiography did not indicate any significant increase in the extent of the lesion, which remained confined to the macula. A survey of the patient's family revealed no characteristic macular lesions; however, 1 brother had extensive drusen of both fundi, a widespread atrophy

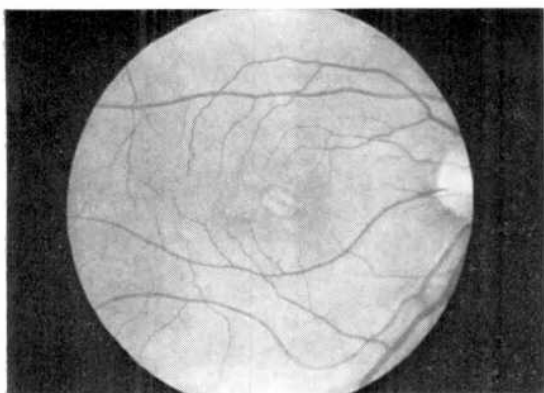


Fig. 7 Photograph right fundus, patient 2 (1975). Faint white plaques surround a circular zone of pigment epithelial atrophy.

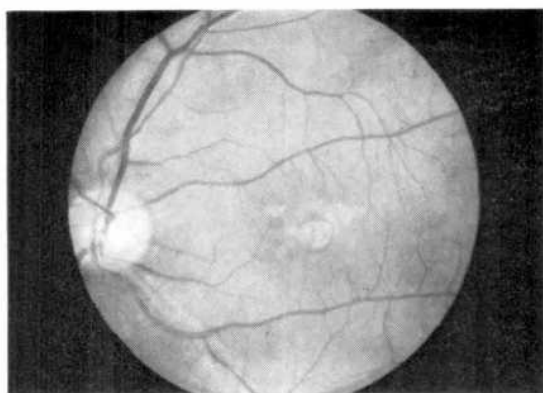


Fig. 8 Photograph left fundus, patient 2 (1975). Well defined white plaque-like lesions radiate from a central circular area of pigment epithelial atrophy.

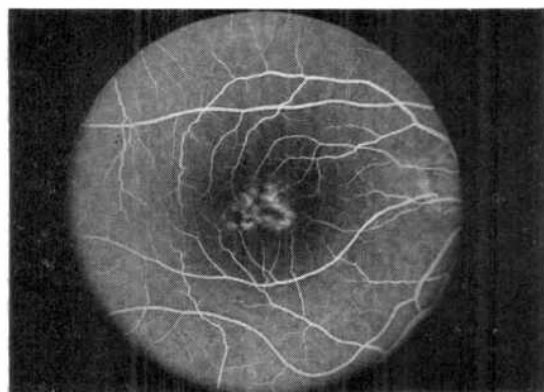


Fig. 9 Venous phase fluorescein angiogram of fundus shown Fig. 7. Discrete pigment epithelial defects fluoresce brightly.

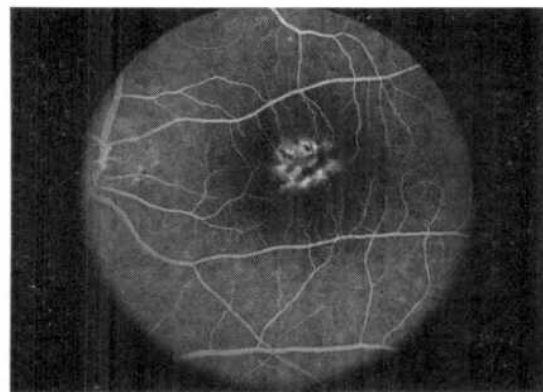


Fig. 10 Late-phase fluorescein angiogram of fundus shown Fig. 8. The plaque-like lesions are mostly hypofluorescent and there is some staining of the affected retinal pigment epithelial layer.

of the RPE, and a visual acuity diminished to 6/24 right and 3/60 left. The patient's father also had poor vision and was able to read only large print using a magnifying glass from the age of 60. The patient's father and mother were first cousins.

PATIENT 3

A 52-year-old male was referred to one of us (I.H.M.) in April 1974. He had noticed about the age of 40 that vision had decreased in each eye. During the 3 years prior to presentation, he had been treated for asthma with prednisone 5 mg per day and for kidney stones with allopurinol. On examination the best visual acuity was 6/18 right and 6/12 left. Routine eye examination was normal apart from the changes noted on funduscopy. The right fundus (Fig. 11) showed a pigmented ring of less than 1 disc diameter (DD), within which a thinned retina and choroidal vessels were seen

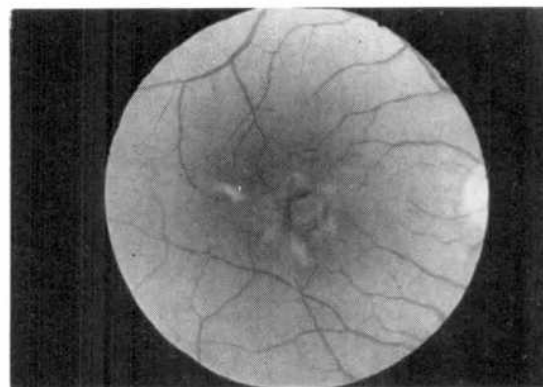


Fig. 11 Fundus photograph right eye, patient 3. A pigmentary ring delineates a central area of retinal pigment epithelial atrophy. Yellow stripes are radially arranged around the atrophic zone.

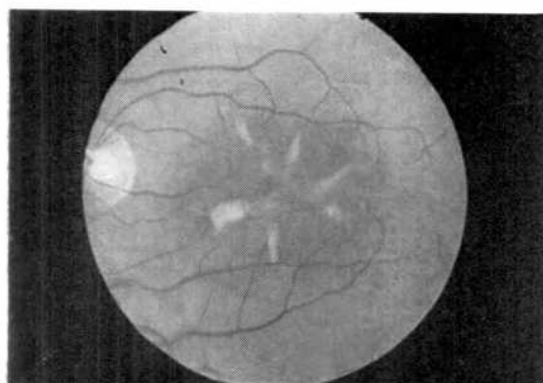


Fig. 12 Left fundus photograph, patient 3. Radiating yellow stripes are arranged around the fovea in a petaloid fashion.

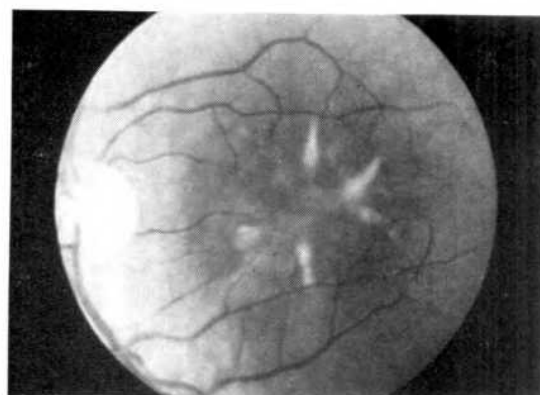


Fig. 13 Left fundus photograph, patient 3, taken 20 months after fundus photograph shown in Fig. 12. The 11 o'clock stripe has faded leaving a pigmentary line. The 4 o'clock stripe may have extended (some artefacts are present).

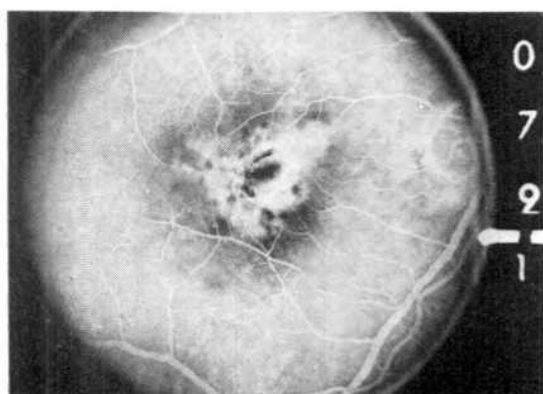


Fig. 14 Late phase fluorescein angiogram of fundus shown in Fig. 11. The yellow stripes are hypofluorescent and are highlighted against the hyperfluorescent pigment epithelial defects.

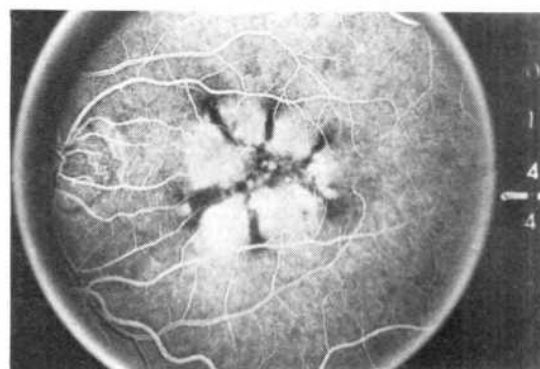


Fig. 15 Early venous phase angiogram of fundus shown in Fig. 12. The yellow stripes are strikingly hypofluorescent or nonfluorescent.

with the slit-lamp. Around the pigmented ring the retina showed a greyish yellow material deposited in a radial fashion deep in the retina or at the level of the RPE.

The left macula (Fig. 12) also demonstrated yellowish deep-seated deposits which were more distinct than those noted in the right fundus. The abnormal material radiated in a petaloid fashion from the region of the left fovea. There was no evidence of microcystoid degenerative changes. Over a period of 20 months 1 of the deposits (noted at 11 o'clock) partially faded, leaving a deep-seated pigmentary line (Fig. 13).

During fluorescein angiography the right macula (Fig. 14) showed a central dark zone within the pigment ring noted on ophthalmoscopy. This, in view of the biomicroscopic findings, suggested a

localised atrophy of the choriocapillaris. Peripheral to the ring a 10° wide circle of hyperfluorescence was evident. Stripes of hypofluorescence corresponded more or less to the yellow deposits highlighted on the hyperfluorescent background. On the left side (Fig. 15) fluorescein angiography showed six non-fluorescent, radially orientated stripes contrasting against the hyperfluorescent background.

Patient 3's 54-year-old only brother noticed decreased vision in his left eye at age 26. Vision is thought to have been stable since. There was no metamorphopsia or photophobia; however, the patient admitted to some degree of night blindness. Routine ocular examination showed no structural abnormalities apart from the lesions noted at the fundi. The corrected visual acuity was 6/7.5 right and 6/36 left. The right fundus showed a small

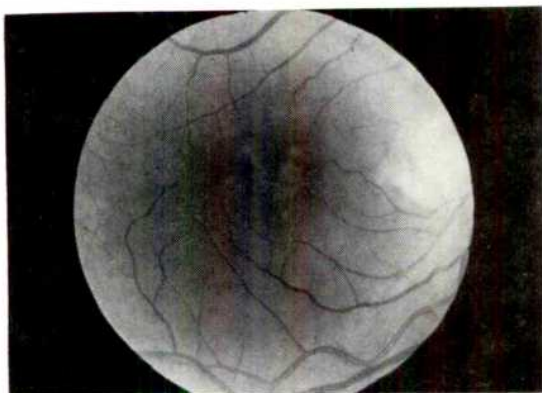


Fig. 16 Right fundus photograph of patient 3's brother. There is a small perifoveal atrophic area. Ill-defined yellow deposits are present and a zone of peripapillary atrophy is noted.

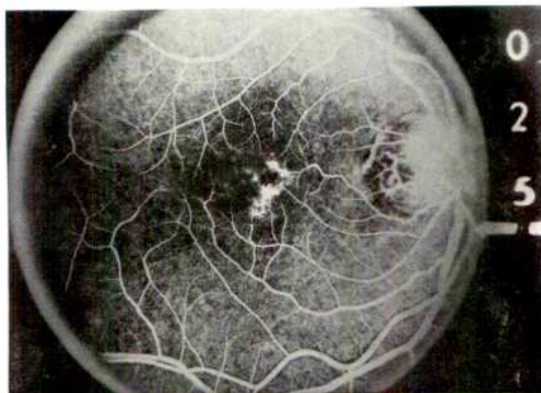


Fig. 17 Mid venous phase angiogram of fundus shown mid venous. There are discrete hyperfluorescent pigment epithelial defects. The yellow plaques are hypofluorescent.

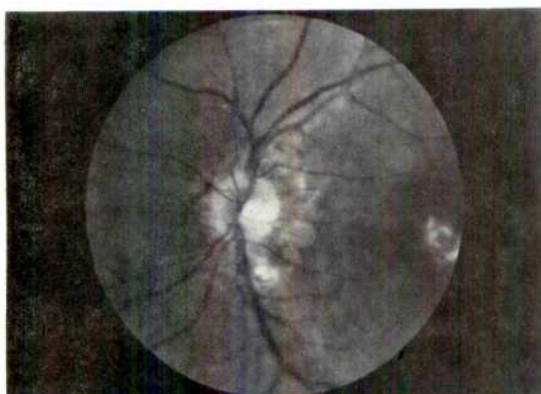


Fig. 18 Left fundus photograph patient 3's brother. There is marked peripapillary chorioretinal atrophy and a macular scar.

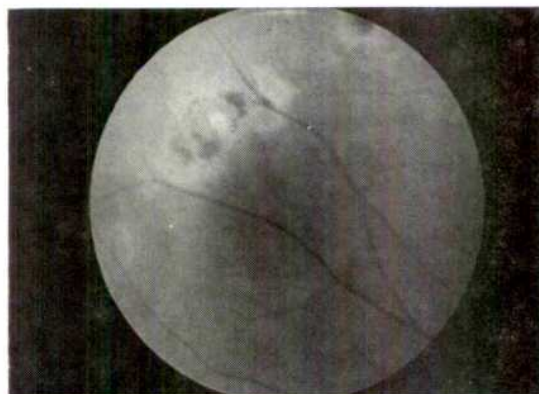


Fig. 19 Left superonasal peripheral fundus patient 3's brother. Postequatorial pigmented lesions are present.

circular zone of retinal atrophy nasal to the fovea. There were some ill-defined stripes of yellow deposits which were hypofluorescent during fluorescein angiography (Figs. 16, 17). The left fundus showed an atrophic maculopathy with peripapillary choroidal atrophy and peripheral postequatorial pigmented lesions (Figs. 18, 19, 20), a picture reminiscent of the presumed ocular histoplasmosis syndrome. During angiography a focal area of hyperfluorescence was noted at the left macula indicating a defect of the retinal pigment epithelium (Fig. 20).

No abnormality was detected on routine examination of patient 3's three children except for 2 drusen at the right posterior fundus of his 16-year-old daughter (Fig. 21).

Patient 3's parents were not examined. His father was said to have normal vision, but his

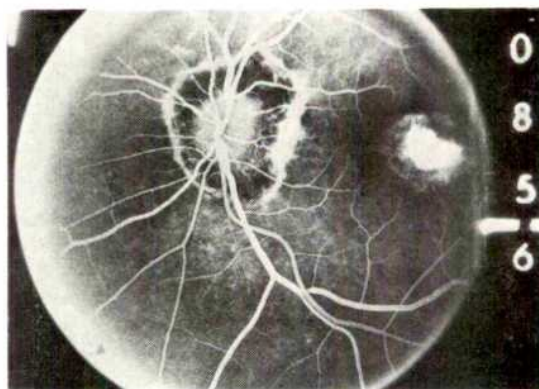


Fig. 20 Late venous phase angiogram of fundus shown mid venous. There is striking peripapillary and macular hyperfluorescence. The features are reminiscent of the presumed ocular histoplasmosis syndrome.

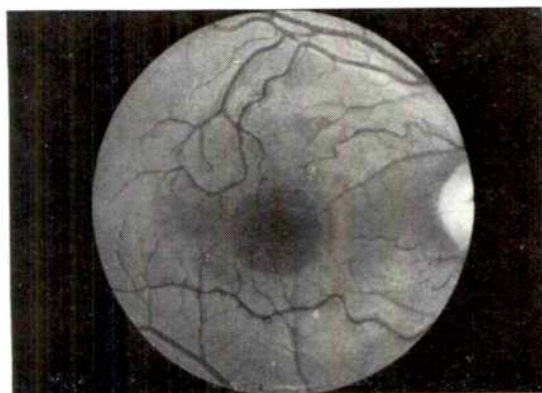


Fig. 21 Right fundus photograph of 16-year-old daughter of patient 3. Two small drusen are present below the macula.

mother used a magnifying glass in addition to her bifocals after the age of 60.

Extensive psychophysical tests were performed by one of us (K.F.) on patient 3, his brother, and his 3 children. The perimetric studies were done with the Tübinger and Ferre-Rand perimeters. Essentially, they showed central scotomas in the 2 brothers and relative parafoveal scotomas in patient 3's daughter. The dark adaptation curves with the Tübinger perimeter were somewhat subnormal in the 2 brothers, in accordance with the symptoms. Colour tests were within normal limits except for the left eye of the brother.

The ERGs were recorded by one of us (P.S.). A modified Rabin and Berson's technique⁶ was used. They showed reduced amplitudes and prolonged implicit times of both photopic and scotopic ERGs in patient 3 and his brother. ERGs were normal in the children. Normal EOG ratios were found in both brothers.

Discussion

Three patients with unusual but characteristically patterned lesions of the macula are presented. The patients are all male and suffered only mild, moderate, or no disturbance of visual functions. The exact age of onset of the lesions was difficult to establish, but it probably occurred between the ages of 30 and 50. The basic abnormality was an oval or oblong, yellow, plaque-like lesion confined to the macular area. The plaques were multiple, relatively discrete, about one-third to one-half a disc diameter in size, and typically arranged in a radial pattern about the fovea. Fundus biomicroscopy and stereophotography confirmed that the lesions were slightly elevated and located at the

level of the RPE. The neighbouring retina showed a variety of RPE changes, some atrophic and some proliferative. The earliest lesions, which were usually asymptomatic, had a uniform yellow-white hue, but with time usually faded, disappeared, or were replaced by an area of RPE atrophy or proliferation. A circular area of atrophic retinal pigment epithelium characteristically developed at or near the fovea in all cases, and at this stage there was generally some abnormality of central visual function. Other changes included circular areas of retinal thinning and choriocapillaris loss. In 1 patient fresh macular and extramacular lesions developed over a period of 2 to 3 years. These additional lesions had identical characteristics to those plaques noted at initial examination.

The existence of some similar lesions in the right eye of patient 3's brother suggests that the condition may be familial, but it is not possible from the current data to establish a mode of inheritance. It is left to other workers in the future to be more explicit on the genetics, if indeed further cases would confirm our present strong suspicion that it is a heritable condition.

No histopathological studies have been undertaken of the lesions in question and their exact nature is not known. However, ophthalmoscopic and angiographic evidence suggest that the disease primarily affects the RPE, and the typical yellow plaques probably represent a deposition or accumulation of some substance within the RPE or in its immediate vicinity. Despite the discrete morphology of the individual plaques there is reason to suspect a diffuse abnormality of the RPE in some patients on account of the widespread abnormalities on fluorescein angiography and the significant EOG findings. The retinal receptors appear relatively unaffected, at least until late in the disease process.

The lesions described are distinctive and morphologically different from the other varieties of patterned dystrophy of the macula. The radially arranged yellow plaques are not typical of the reticular dystrophies or the butterfly dystrophy of the fovea, and no atrophic changes have been described in latter conditions. The yellow plaques resemble confluent drusen in that they occur at the level of the RPE, are discrete, and predominantly affect the posterior fundus. However, the yellow plaques show little tendency to enlarge concentrically and are characteristically hypofluorescent during angiography. The radial disposition of the subretinal plaques is quite different from the general distribution of drusen, and no obvious decompensation of the retinal pigment epithelial barrier or development of a disciform response has been noted.

The lesions characteristic of patterned dystrophy

described in this report also differ fundamentally from those typically of fundus flavimaculatus in their hue, size, and distribution. The yellow patterned lesions show some of the characteristics of the deposits encountered in vitelliform macular degeneration (Best's disease). They are both yellow, situated at the level of the RPE, and associated with relatively mild changes in central visual functions. The appearance of fresh lesions at the posterior pole of the eye during the evolution of the yellow plaques may also occur in vitelliform macular degeneration. The patterned dystrophy, however, differs from vitelliform macular degeneration in that there is no evidence of a yolk-like lesion at any stage of the disease process or layering of the abnormal deposits. In addition the electrooculographic changes in vitelliform macular degeneration are more uniform and severe than those noted in our patients.

A peculiar foveomacular dystrophy described by Gass⁷ shows some of the clinical characteristics of the patterned dystrophy reported in this paper. In both groups of patients the condition began between 30 and 50 years of age and affects vision relatively slightly. The lesions in both conditions are sub-retinal, symmetrical, and slowly progressive. The lesions described by Gass, however, are less regular, not disposed in a petaloid pattern, and have a uniform, central pigmented spot at the fovea. In addition many of his cases are also associated with a more widespread disturbance of the RPE and to some degree resemble hereditary drusen.

Singerman *et al.*⁸ have recently described a macular dystrophy in a large sibship and labelled the condition dominant slowly progressive macular dystrophy. Some of the patients described in this report have macular lesions resembling the yellow

plaques described above and showed similar angiographic features. It may be that there is some overlap in the cases described in our report and certain of the members of their large sibship.

Although the patterned dystrophy with yellow plaques and atrophic changes resembles several well documented focal abnormalities of the RPE, it nevertheless has distinct morphological characteristics, a natural course and fundus findings, and it is probably justifiable to consider it as a separate clinical entity. The yellow plaques almost certainly relate to an abnormality or malfunction of the RPE and as such probably form a small part of the wide spectrum of conditions which reflect a malady of this highly specialised layer.

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Diced cartilage grafts to correct enophthalmos

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SUMMARY A technique is described using diced cartilage grafts to correct the volume deficit which is responsible for many of the unsatisfactory cosmetic features following enucleation.

Cosmetic defects following enucleation and evisceration are distressingly common. In severe cases 4 elements contribute to the abnormal appearance: enophthalmos, deepening of the superior sulcus, ptosis, and lower lid laxity. All except the lower lid laxity can be attributed to the loss of volume of intraorbital contents that follows removal of the globe. The purpose of this paper is to describe a technique for introducing diced cartilage chips into the orbit to correct the deformities resulting from loss of intraorbital tissues.

Methods

The principle of the procedure is to increase the volume of the orbital tissues by introducing costal cartilage.

REMOVAL OF COSTAL CARTILAGE

An incision 10 cm long is made along the costal margin, the medial end of the incision being 2.5 cm from the midline. The incision is made through the skin, subcutaneous tissue, and deep fascia, and the rectus abdominis muscle is retracted medially to expose the lower costal cartilages.

An incision is made in the perichondrium of the central cartilage, usually the sixth, and elevated from its anterior and posterior surface. Care must be taken when working behind the cartilage not to penetrate the pleura. The costal cartilage is removed by cutting it at each end with a rib cutter. A piece of costal cartilage 5 cm in length is usually sufficient. The perichondrial sheath is sutured with 4-0 plain catgut, and the wound is closed in layers.

INSERTION OF THE GRAFT

An incision is made along the central third of the

inferior orbital margin. The periosteum is incised and elevated off the floor back to the apex of the orbit. A small-bore cannula with internal trochar (as used for tapping fluid from the chest or peritoneal cavity) is passed along the orbital floor to the apex of the orbit and then pushed up through the periosteum. The cartilage is then diced to allow its introduction into the orbit through the cannula, the trochar being used to push the cartilage through the cannula. The artificial eye is left in place for the procedure, and enough cartilage is introduced to overcorrect the deformity slightly. The periosteum is sutured with plain catgut, and the orbicularis sutured as a second layer and the skin closed with a subcuticular monofilament nylon suture. A firm bandage is applied to minimise postoperative oedema.

Results

We have performed this operation without complication on 8 patients with cosmetic deformity following enucleation, and the results are satisfactory in all cases. The improved appearance has been maintained without any observable absorptions of the implant over the follow-up period, which is 8 years in 2 of the cases.

Discussion

The major advantages of this technique over the more commonly employed methods are due to the use of a diced cartilage autograft rather than the widely practised techniques involving implantation of synthetic materials (Sugar and Forestner, 1946; Vannas, 1958; Hill and Radford, 1965; Hill, 1967; Shannon, 1967; Smith *et al.*, 1967) or grafts of bone or fascia (Devoe, 1945; Cutler, 1946; Vannas, 1946; Gordon Cole, 1967) or large pieces of cartilage, which are liable to resorb.

Synthetic materials excite an inflammatory

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response (Ben-Hur, 1967) and have a tendency to migrate (Iliff, 1967). Of the various materials employed for orbital prostheses injectable silicone is probably the most satisfactory (Soll, 1971) but is not without its complications.

Cartilage has considerable advantage over bone. Unlike bone grafts, cartilage grafts survive equally well whether in contact with like tissue (cartilage) or some other tissue such as fat, muscle, or fascia (Peer, 1954). Functional stresses seem important for the survival of autogenous bone grafts but are unimportant for cartilage grafts, which survive and usually maintain their bulk regardless of function.

Histological examination of diced cartilage grafts (Peer, 1939, 1943) after transplantation shows that the spaces between the cartilage are at first occupied by haematoma that organises. The cartilage chips rest against each other, separated by a small area of connective tissue, and contraction is minimal. Diced grafts thus occupy a larger space than the solid rib cartilage from which they are derived. Histological sections show the survival of chondrocytes within normal matrix and general absence of connective tissue invasion and absorption.

The use of costal cartilage has the obvious advantage that it is easily obtained in quantities adequate for the procedure, and can be diced easily for introduction through the cannula.

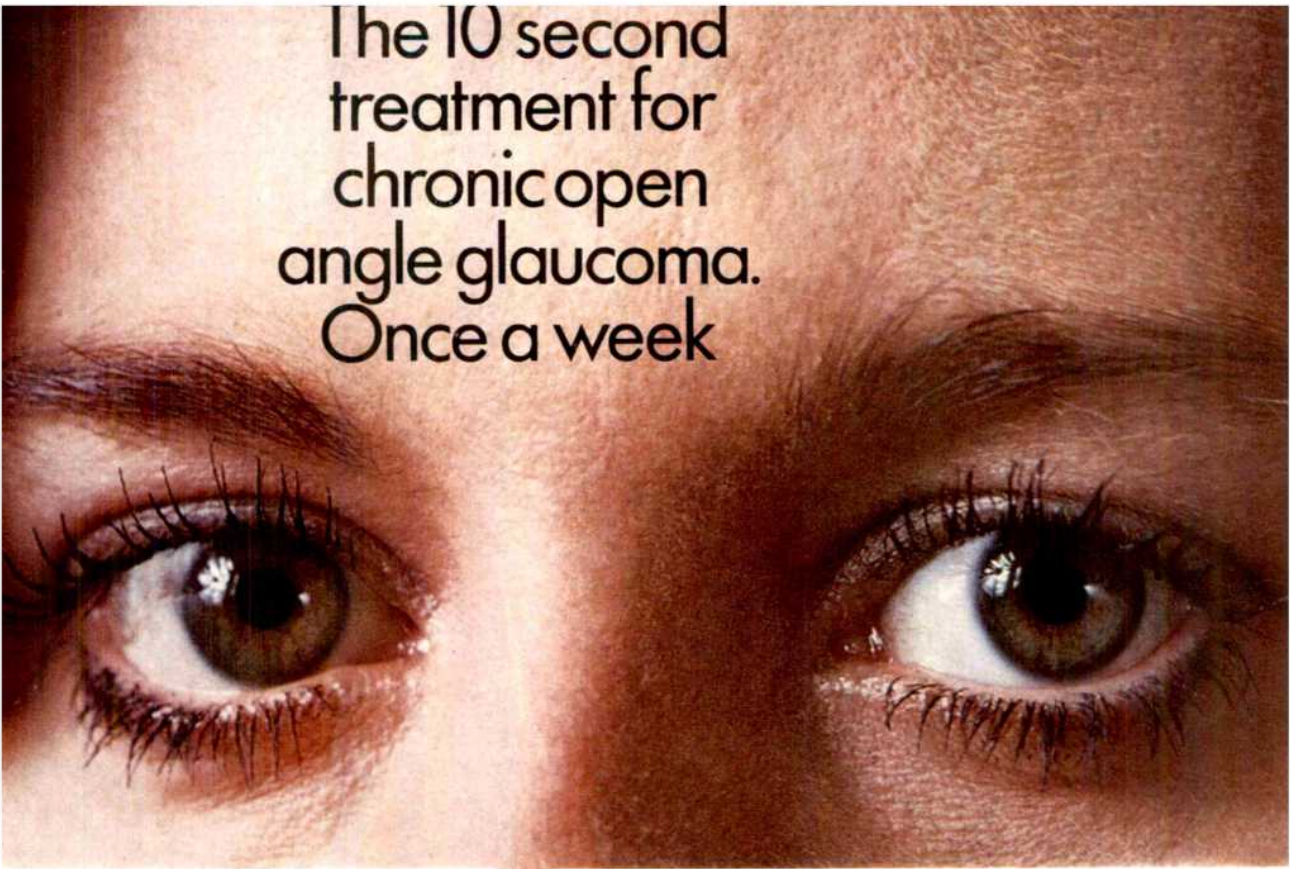
The small incision in the inferior orbital margin can be easily hidden in a skin fold, and the subperiosteal route along the orbital floor provides easy access to the orbital apex, the periosteum healing back on to the bone of the orbital floor and sealing the tract made by the trochar and cannula. Migration of cartilage fragments has not been a problem. Using a trochar and cannula ensures that cartilage is diced to such a small size that the fragments are unlikely to resorb. There is the additional advantage that the cannula can be left in situ for the entire procedure, avoiding the need for repeated instrumentation when introducing fragments and avoiding the need for retraction of tissues which is traumatic and results in oedema and distortion.

This technique can be used only on patients who have an enophthalmic prosthesis or blind eye. Because of the obvious danger to structures in the

apex of the orbit it is a technique which cannot be employed when the orbit contains an eye with useful vision.

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A close-up photograph of a person's eyes, looking directly at the camera. The eyes are brown with long, dark eyelashes. The skin around the eyes is fair and slightly wrinkled.

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Dosage and Administration
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Self-medication with pilocarpine among outpatients in a glaucoma clinic

S. E. NORELL AND P.-A. GRANSTRÖM

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SUMMARY A recording medication monitor and fluorescein technique were used to study self-medication by 82 patients with primary open-angle glaucoma for whom pilocarpine eye drops 3 times a day had been prescribed. Of these patients 34 (41%) missed 6 or more doses during a 20-day period, and for 35 (43%) an 8-hour dose interval was exceeded at least 20% of the time. Consequences may include lack of effectiveness in preventing visual loss and unnecessary prescription of more potent, and more toxic, drugs.

About 50% of patients on long-term medication do not take their drugs as prescribed (Sackett and Haynes, 1976). This may be one of the major reasons for failure of treatment in such conditions as hypertension (Sackett *et al.*, 1975), heart failure (Johnston *et al.*, 1978), and tuberculosis (Dixon *et al.*, 1957). We have reviewed the development of visual field defects over a 2-year period among 40 patients with primary open-angle glaucoma treated at the eye clinic of our hospital. Of these patients 18 (45%) have shown marked progression of their visual field defects despite continuous prescription of drug treatment.

Primary open-angle glaucoma often causes only marginal complaints but requires long-term and frequently inconvenient treatment. Treatment is aimed at preventing long-range damage and provides no subjective improvement to prove its benefit to the patient. In fact, drug treatment may even produce temporary symptoms, such as smarting or blurred vision. Nevertheless patients are expected to take their medication regularly. Moreover, taking the drugs regularly may be of particular importance in glaucoma treatment since the drugs commonly used, such as pilocarpine, have a relatively short duration of action (Ellis, 1977). Self-medication has been called 'the most overlooked aspect of glaucoma' (Riffenburgh, 1966).

Some interview data are available on the medication behaviour of glaucoma patients. Vincent (1972) interviewed 62 glaucoma patients and 36

(58%) said they failed to take their eye drops more often than once a month. In a study of 40 patients with chronic simple glaucoma interviews indicated that 11 (28%) missed properly taking their medication more often than once a week (Bloch *et al.*, 1977). In another study 94 glaucoma patients were asked, 'Why don't you take the eye drops exactly as the doctor said?' and 31% 'admitted incorrect usage of medications' (Spaeth, 1970). The phrasing of the questions in these studies and some of the comments made by the authors point out the difficulties in obtaining accurate information on medication behaviour by interview. Indeed, striking discrepancies have been found between interviews and more objective data on drug taking by patients on different kinds of medication (Bergman and Werner, 1963; Gordis *et al.*, 1969; Roth and Caron, 1978). In ophthalmology, however, there is little objective information on medication behaviour. Self-medication of 2 patients with glaucoma using a medication monitor technique has been described (Yee *et al.*, 1974). The purpose of the present study was to describe medication behaviour with pilocarpine eye drops among patients with primary open-angle glaucoma treated in an eye clinic.

Material and methods

STUDY SAMPLE

Included in this study were all patients treated at the eye clinic of Huddinge University Hospital by 1 March 1977 who fulfilled the following 6 criteria in their medical records: (1) diagnosed as primary open-angle glaucoma with (2) glaucomatous visual field defects, (3) glaucomatous cupping of the optic

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disc, and (4) intraocular pressure above or equal to 21 mmHg recorded at least twice in the same eye; (5) prescription of 4% pilocarpine eye drops 3 times a day, and (6) visual acuity of at least 2/60 in a pilocarpine treated eye.

Of the 92 patients fulfilling these criteria 10 were lost before they were studied. (Data were collected between March 1977 and November 1978.) One patient was lost because he moved abroad, 3 because they died, 3 because their therapy was changed, and 3 for psychological or psychiatric reasons. The latter 3 refused to visit the clinic and had been out of eye drops for long periods of time during the past years. Medication behaviour of the remaining 82 patients (45 men and 37 women) was studied. Their ages varied between 56 and 90 (median 73) years.

MEASUREMENT METHODS

Self-administration of pilocarpine eye drops was studied with a medication monitor and fluorescein technique. These methods have been described and discussed elsewhere (Norell *et al.*, 1979).

The medication monitor consists of a small plastic box with a holder for a 25 ml medication bottle. An elastic flap linked to a microswitch signals to the electronic part of the monitor whether the eyedropper cap is on or off. The information on whether or not the bottle has been opened during the last hour is transferred to a Random Access Memory with a capacity of 511 hours. By connecting a separate read-out device an electrocardiographic recorder can be used to display a record of the total register content together with a time signal.

The monitor recorded the date and hour each time the medication bottle was opened during a 3-week period between visits to the eye clinic. The days of clinic visits were excluded, leaving a monitor record of 20 days for each patient. For 8 patients a monitor record was obtained only after a second 20-day period owing to defective monitor batteries during the first test period. The patients were not told the purpose of the monitor until the collection of data was completed. Informed consent was obtained from the patient before the monitor record was printed out by computer and analysed, and the procedures were approved by the committee on ethics. To control other sources of the drug all prescriptions and bottles of pilocarpine were recalled from the patient when he received the monitor. No further intervention in the patient's routine was made until the monitor data were collected.

A fluorescein technique was used to study the ability of patients to administer the eye drops into the conjunctival sac. Each patient was asked to

apply eye drops, containing 0.04% fluorescein, 5 different times in each eye, giving 10 tests of whether or not these drops actually fell into the conjunctival sac. Of the 82 patients studied, 15 patients, according to interview, always had their pilocarpine eye drops administered by somebody else (5 by a nurse and 10 by relatives). These patients were not examined with the fluorescein technique. Another 3 patients were lost to the study before they were tested with the fluorescein technique.

MEASURES OF MEDICATION BEHAVIOUR

The intervals between doses is a fundamental measure of medication behaviour, which in turn depends on the number of doses taken as well as the spacing between doses. The monitor records provide information on the length of the intervals between openings of the medication bottle. Such intervals will represent dose intervals under certain conditions (Norell *et al.*, 1979). Monitor data, therefore, may be presented as a frequency distribution of dose intervals, as in Table 1, where x is the length of dose intervals in hours. If we choose arbitrarily any specific interval length of t hours, then the sum of $(x-t)$ for all intervals where $x > t$ will give the total time exceeding the t hours dose interval during the observation period. Dividing this sum by the length of the observation period, gives the *proportion of time exceeding the t hours dose interval*.

This may also be illustrated graphically in a cumulative frequency curve based on the same monitor data (Fig. 1). A vertical line representing a certain interval length (t), such as the line $t=8$ in Fig. 1, will divide the area over the curve into 2 parts, A and B. The proportion of time exceeding t hours dose interval is equal to $A/A+B$. This proportion may be determined for t =the drug's duration of action, thus estimating the proportion of the time when there is no drug effect. It may also be determined for $t=24/n$, where n is the number of daily doses prescribed, thus estimating the proportion of time exceeding the duration of dose intervals expected if all prescribed doses had been taken at equal intervals. Since in this study all patients had a prescription of pilocarpine eye drops 3 times a day, the proportion of time exceeding 8-hour dose interval was estimated.

Monitor data were also analysed in relation to the number of daily doses prescribed. For each patient there was an interval during the night (between 0100 and 0400) when no doses were taken. For each day (between 2 such intervals) the number of doses taken (d) was compared to the prescribed 3 doses a day. If $d < 3$, then $(3-d)$ is the number of missed doses that day. If $d > 3$, then

(d-3) is the number of extra doses that day. The number of missed doses during the 20-day period was calculated for each patient and divided by the number of doses prescribed for that period ($20 \times 3 = 60$). This gives the *proportion of missed doses* for each patient. Similarly the number of *extra doses* was calculated.

Results

One patient had 8/10 positive fluorescein tests. All other patients examined with the fluorescein technique had 10/10 positive tests, indicating that they themselves were able to administer the eye drops into the conjunctival sac. This somewhat unexpected finding may reflect their experience in taking eye drops after 0.5 to 23 (median 4.4) years of glaucoma treatment.

Monitor data are given in Table 1 as the frequency distribution of the duration of intervals between doses in hours for the patient sample. Fig. 1 is a cumulative frequency curve from Table 1. Intervals between doses varied from 1 to 164 hours with a median of 8 hours and a maximum frequency at 6 hours. Of the 4542 dose intervals 840 (18%) had a duration of 12 hours or more and 509 (11%) had a duration of 4 hours or less.

For the study sample the proportion of time exceeding the t hours dose interval was 21% for $t=8$ (that is, 21% of the observed time was more than 8 hours from a previous dose), 11% for $t=10$, 6% for $t=12$, and 4% for $t=14$. Fig. 2 shows the proportion of time exceeding 8 hours dose interval for each patient in the study sample. This proportion varied from 3% to 88% with a median

of 17.2. For 35 (43%) of the 82 patients at least 20% of time was more than 8 hours distant from a previous dose.

In Fig. 3 the proportion of missed doses is given for each patient, which varied from 0 to 83% with

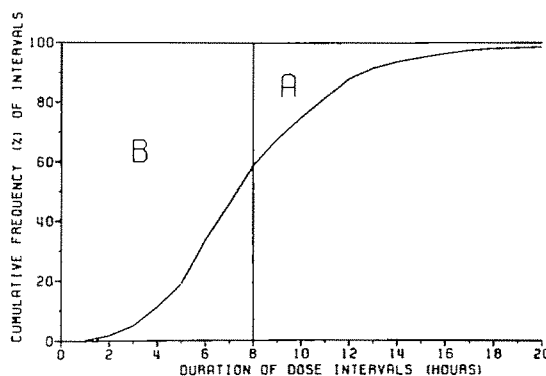


Fig. 1 Cumulative frequency distribution of dose intervals; from Table 1 (see text)

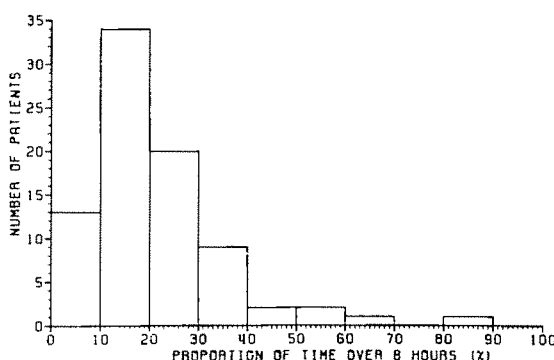


Fig. 2 Proportion of time exceeding 8-hour dose interval for each patient in the study sample ($n=82$)

Table 1 Frequency distribution of dose intervals in hours for the study sample ($n=82$) during 20 days' medication

x	f	x	f	x	f
1	8	15	65	32	3
2	73	16	61	33	1
3	139	17	49	34	1
4	289	18	28	35	1
5	352	19	11	43	1
6	663	20	11	47	1
7	555	21	6	48	4
8	591	22	6	60	1
9	403	23	6	88	1
10	327	24	14	107	1
11	302	25	4	121	1
12	289	26	7	123	1
13	168	27	1	152	1
14	93	28	2	164	1

x = Length of intervals between doses (in hours). f = Number of dose intervals recorded by the monitor.

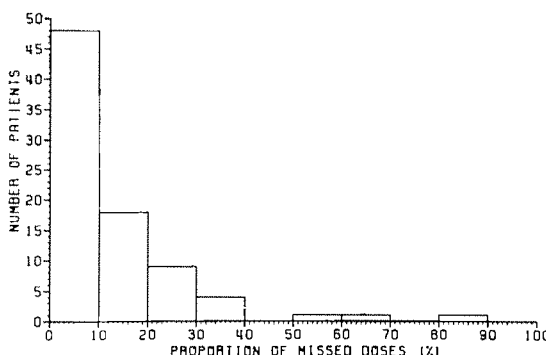


Fig. 3 Proportion of missed doses for each patient in the study sample ($n=82$). Of the 48 patients who missed less than 10% of the doses prescribed 21 missed no doses and 43 missed less than 5% of doses

a median of 3.3%. Of the 82 patients studied 34 (41%) omitted at least 10% and 16 (20%) omitted at least 20% of the prescribed doses. The total number of missed doses in the study sample was 507, or 10% of the doses prescribed. Similarly, the total number of extra doses was 50, or 1% of the doses prescribed, varying between 0 and 12% for individual patients.

The proportion of time exceeding the 8-hour dose interval is determined not only by the number of doses taken but also by the spacing between doses. This is evident in Table 2, where the proportion of missed doses is related to the proportion of time exceeding the 8-hour dose interval. For example, among the 21 patients taking all the prescribed doses, 14 exceeded the 8-hour dose interval at least 10% of the time owing to irregular spacing between doses.

Discussion

Some problems in the measurement of medication behaviour were discussed in a previous paper (Norell *et al.*, 1979). It was concluded that the medication monitor and fluorescein technique offer more accurate and detailed information on medication behaviour than, for example, similar data obtained by interview.

The effect of drug treatment is related not only to the number of doses taken but also to the spacing between doses. Finding a measure which takes both these factors into account is a major problem in describing medication behaviour. The proportion of time exceeding a t hours dose interval offers a solution to this problem. It has been suggested that a single dose of pilocarpine is effective in lowering intraocular pressure for about 8 hours or less (Ellis, 1977; Heilmann and Richardson, 1978), while some data indicate a longer duration of action (Drance *et al.*, 1974; Quigley and Pollack, 1977). On the assumption that the effective duration is about 8 hours, it would seem reasonable to consider the proportion of time more than 8 hours from a

Table 2 Missed doses in relation to time exceeding 8-hour dose interval for each patient in the study sample

Time over 8 hours (%)	Missed doses (%)				Total
	0	1-	10-	20-	
0-	7	6	0	0	13
10-	12	17	5	0	34
20-	2	2	10	6	20
30-	0	2	3	10	15
Total	21	27	18	16	82

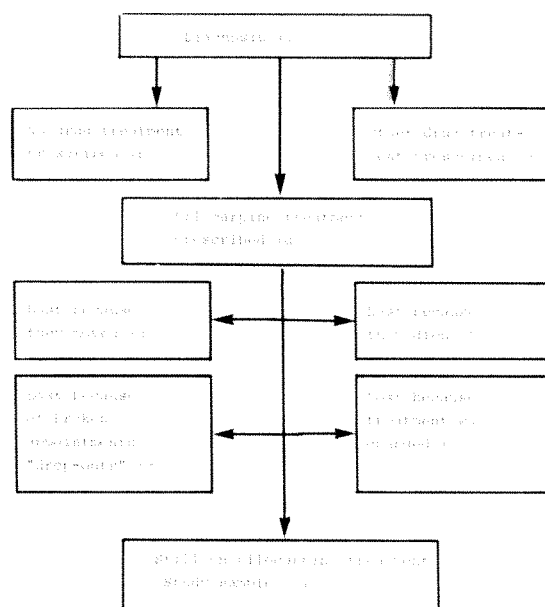


Fig. 4 Selection process forming clinical study sample (see text)

previous dose as a rough estimate of the proportion of time when there is no drug effect. However, a more accurate description of the time without drug effect would have to take several factors into account. First, drug effect is not an all-or-nothing phenomenon, and the effect of a single dose will decrease gradually over time. Secondly, if several doses are taken with shorter intervals, say 1 or 2 hours, the concentration of the drug in the anterior chamber of the eye may rise above the concentration followed by a single dose, and this may give a longer 'duration' after the last dose. Thirdly, if the level of the intraocular pressure (IOP) is important as a cause of visual loss in glaucoma, and if, for example, IOP is higher during the morning hours than later during the day, then it may be more important to 'cover' these hours. A further refinement of the measure used here will have to take these and possibly other factors into consideration.

From the patients diagnosed and for whom pilocarpine was initially prescribed the study sample was selected by the process summarised in Fig. 4. After diagnosis (a) pilocarpine treatment is prescribed for some patients (d) but not for others (b, c). Of the patients for whom pilocarpine treatment was prescribed some will have their therapy changed to other drugs, for example, phosfoline iodide, or operation (h). In this study 3 patients were lost because their treatment was changed between 1 March 1977 and their entry into the study (median

time about 10 months). Over many years a considerable proportion of patients initially on pilocarpine have their treatment changed. Since the reason for this may be that the pilocarpine treatment did not work, an overrepresentation of patients not adherent to the prescribed regimen should be expected in this group. Other patients will be lost because they have not maintained follow-up appointments (g). In this study 3 patients were lost during the time before their entry into the study. For long periods of time they did not visit the clinic, had no supply of pilocarpine, and were obviously not taking the drug. Other studies have shown that 37% of patients with glaucoma or ocular hypertension did not return for follow-up appointments during 12 to 20 months after initial diagnosis (Bigger, 1976) and that among patients referred for further testing from a glaucoma screening programme 20% did not keep their appointment (Rosenthal, 1967).

The selection process forming a group for clinical study is of course more complicated than it would appear from the diagram. In any case a considerable proportion of the patients for whom pilocarpine was initially prescribed were lost in the process. Furthermore, an overrepresentation of patients not adherent to the prescribed regimen would be expected among those lost from the sample selected for study. A follow-up study of an inception cohort, that is, patients for whom pilocarpine was initially prescribed from a well defined population, might clarify this situation.

Our findings suggest that missed doses are more frequent than has been found in other studies of medication behaviour in glaucoma (Spaeth, 1970; Vincent, 1972; Bloch *et al.*, 1977). This is not surprising, since these studies have been based on interview data, with underreporting of missed doses as a major problem (Bergman and Werner, 1963; Gordis *et al.*, 1969; Roth and Caron, 1978). In addition, our data show that dose intervals exceeding the expected interval length will often be due to irregular spacing between doses rather than omitted doses. The proportion of time exceeding an 8-hour dose interval varied widely between patients, from 3% to 88%, with a median of 17.2%. Furthermore, the study sample could be expected to be more adherent to the prescribed regimen than the patients for whom pilocarpine was initially prescribed.

Visual loss from glaucoma during drug treatment is often dealt with by prescribing more potent, and more toxic, drugs. This may not be appropriate, since lack of effect in preventing visual loss may be due to irregular drug taking rather than that the drug is not effective. Similarly, the outcome of

clinical drug trials may be influenced by the patients' medication behaviour. This calls for simple methods to check that patients take their drugs regularly, and useful strategies to improve medication behaviour. These problems are under investigation in our group.

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Book reviews

Catalog of the Bernard Becker, MD, Collection in Ophthalmology. Pp. 102. \$12.50. Washington University: St. Louis. 1979.

This is a catalogue of over 600 volumes on historical ophthalmology from the unique collection which Bernard Becker has presented to the Washington University Medical School Library. It includes a note of all the pre-1850 books and important historical texts from after that date, with collations, references, a brief evaluation of the book, and microfiches of all the title pages. The presentation is superb. The type face, paper, decorative illustrations (also from the Becker collection), and general lay-out are exemplary. The book is a pleasure to handle, which will be an added reward for those specialist libraries (and the even more select band of cognoscenti) for whom it is written. P. D. TREVOR-ROPER

Current Research in Ophthalmic Electron Microscopy. Vol. 2. Ed. MANFRED SPITZNAS. Pp. 216. DM48. Springer-Verlag: Berlin. 1978.

The contents of this book represent the proceedings of the second meeting of the European Club for Ophthalmic Fine Structure held in Paris in the spring of 1978. Individual papers range from comparative anatomy to pathology, the latter including aspects of both experimentally induced and naturally occurring ocular disease.

As with the proceedings of most meetings, many of the topics have been or can be expected to be presented elsewhere in the body of ophthalmic literature, but it is useful to have so many papers with a common theme drawn together in this way, especially as they generally observe a high standard of scientific validity and clinical relevance. There can be no hesitation in recommending this book to all who are involved in the morphological study of the eye and its diseases.

Having declared my enthusiasm for this publication I do, nevertheless, have reservations as to the value of research which is artificially limited to a single technique. It is by study based on scientific disciplines, and that often multidisciplinary, rather than isolated methods that progress is fastest. An apposite example occurs in an otherwise excellent article on peripheral subretinal neovascularisation: filaments are described in Bruch's membrane with ultrastructural features consistent with elastic-related oxytalan, but because of technical limitations imposed by themselves or the conference the authors cannot do more than speculate. The application of histochemical methods would almost certainly have clinched the matter.

The standard of publication is good, with mostly adequate reproduction of electron micrographs, though here and there it is evident that English is not the first language of either author or editor. Thus on page 178 we gather that specimens of extraocular muscle were obtained from people who had been sacrific(c)ed.

A. GARNER

Atlas der Kontaktlinsen-anpassung. By VON WULF EHRICH. Pp. 169. DM168. Ferdinand Enke Verlag: Stuttgart. 1978.

This atlas on contact lens practice is written in German and contains sections on material, hygiene, fitting of various types of lenses, keratoconus, irregular astigmatism, and the various medical uses of the appliance. The illustrations are excellent and the legends are explicit. While the whole range of contact lens practice is not covered, it may be argued that there are several technical aspects which do not lend themselves to illustrations. The atlas should be used therefore only as a supplement to a contact lens textbook or by practitioners wishing to study illustrations and who are not necessarily directly involved in this speciality.

MONTAGUE RUBEN

Springer Series in Optical Sciences: Frontiers in Visual Science. Eds. S. J. COOL and E. L. SMITH. Pp. 798. \$41.80. Springer-Verlag: New York. 1978.

It is not clear why this collection, which includes some excellent papers, is entitled as above. Some of the work forms the backbone, of current research (for example, papers on the corneal environment, on photoreceptor shedding, on retinotopic organisation, on stereopsis, on cortical edge detectors, on visual experience, etc). Some papers are old hat and have been published before (for example, analysis of colour vision by exchange thresholds, and microspectrophotometry of outer limbs). And some, such as papers on education and health care, have nothing to do with the topic. This means that one has to rummage for the nuggets of gold. Perhaps this explains the word 'frontiers' after all.

As happens so often in such volumes, editing appears in name only. Cross-references, which might help the reader, are omitted, and the standard of the volume is high only because some of the component contributions are good. No reason is given why only some of the discussions are reproduced: all of them were taped. Since no proper editing is undertaken, the reader would benefit if an author's paper were accompanied by the comments of his peers. This said, the book can be recommended as a representative cross-section of current fundamental research in the major fields covering ocular and visual mechanisms and the relevant anatomy. ROBERT WEALE

Die Glaukome in der Praxis. By W. LEYDECKER. Pp. 216. DM19.80. Springer-Verlag: Berlin. 1979.

This small handbook is designed to provide the ophthalmologist with guidelines on the diagnosis and management of glaucoma in all its various forms. The author has combined a review of contemporary investigations and therapy with an assessment of some of the less modern techniques, many of which are now passing into ophthalmic history. It is interesting, for instance, that tonography still merits a whole chapter. The book

is sufficiently up to date to mention some of the new pharmacological preparations such as timolol, and the modern forms of drainage operations are reviewed. The text is completed with a useful bibliography. Professor Leydhecker is to be congratulated on this revision of his previously published handbooks on glaucoma, and this book should make interesting reading for all wanting to learn about the subject.

T. J. FFYTCH

The Macula: A Comprehensive Text and Atlas. By LAWRENCE A. YANNUZZI, KURT A. GITTER, and HOWARD SCHATZ. Pp. 412. \$82.50. Williams and Wilkins: Baltimore, Maryland. 1979.

Now that the initial romance of fluorescein angiography and laser therapy has begun to die down there has been a need, for the past few years, for an ophthalmic textbook which would take a reasoned and well-informed look at macular disease and provide guidelines for both the investigation and therapy of these important conditions. *The Macula* by three co-authors who have worked together on several other projects fulfils this role admirably and is to be highly recommended.

The book incorporates the contributions of many other authors with international reputations and is divided into a series of chapters on the macula and its

diseases. The illustrations rely not surprisingly a great deal on fluorescein angiograms, though colour photographs and red-free pictures are used frequently. The selection of the illustrations is excellent throughout, and simple diagrams are used to augment the information derived from some of the pictures.

The subject of macular disease is dealt with in very broad terms, and most of the clinical manifestations of retinal disease are discussed. This leads at times to repetition, but many readers would find this a useful attribute. There are very few faults in the text itself—a line missing on p. 118, an inverted colour photograph on p. 321, and wrong numbering of Figs. 25.18 and 25.20—but everywhere the text is lucid and the illustrations relevant. A special mention should be made of the final chapter on the evaluation of photocoagulation therapy. Anyone about to embark on a clinical trial of this type of therapy is advised to read it carefully and be reminded of the pitfalls that occur along every step of therapeutic research.

This book makes essential reading for all ophthalmologists, not only those concerned with retinal disease, since macular function performs such an important role in the life of each one of us. The authors and their co-workers are to be congratulated on a very fine achievement.

T. J. FFYTCH

Correspondence

Usher's syndrome

SIR, Fishman *et al.*¹ attempt to correlate age-related loss of central visual acuity in the Usher syndrome with 'quantitative' estimates of 'contributing factors' such as foveal lesions and cataracts in hopes of generating data for the purposes of counselling patients 'as to the potential for visual loss with age'. These authors may have overlooked the most useful and reliable predictor of age-related visual loss in the Usher syndrome, namely, the degree of congenital neurosensory hearing loss. Several investigators have suggested that the Usher syndrome is genetically heterogeneous, with approximately 90% of patients having profound congenital deafness, vestibular dysfunction, and onset of retinal dystrophy before age 10 years, and 10% having some residual hearing with normal vestibular function and onset of retinal dystrophy after adolescence.^{2,3} Although both forms are inherited in an autosomal recessive way, they appear to be two genetically distinct entities that show little overlap between families.

Degree of sensorineural hearing loss and age of onset of symptoms of retinal dystrophy would appear to be better predictors of age-related visual acuity than foveal lesions, since there was not an invariable correlation between decreased visual acuity and foveal lesions in the study of Fishman *et al.*¹ nor was there an attempt to determine the predictive value of a given foveal appearance for visual acuity over time.

Prospective studies to define the natural history of genetic disorders such as the Usher syndrome are badly needed. A 'sampling' of larger numbers of patients will not clarify the natural history unless all possible factors that may predict rate of age-related visual loss are studied.

ROBERTA A. PAGON

Division of Medical Genetics,
Children's Orthopedic Hospital
and Medical Center,
4800 Sand Point Way NE,
Seattle, Washington 98105, USA.

References

- ¹Fishman G, Vasquez V, Fishman M, Berger D. Visual loss and foveal lesions in Usher's syndrome. *Br J Ophthalmol* 1979; **63**: 484-8.
- ²Nuutila A. Dystrophia retinal pigmentosa—dysacusis syndrome (DRD): a study of the Usher—or Hallgren syndrome. *J Genet Hum* 1970; **18**: 57-88.
- ³Davenport SLH, O'Nuallain S, Omenn GS, Wilkus RJ. Usher syndrome in four hard-of-hearing siblings. *Pediatrics* 1978; **62**: 578-83.

SIR, Dr Pagon's remarks refer to our findings on 48 patients with Usher's syndrome. The data which we presented documented central visual loss, quantitatively listed the extent of lens opacities, and described the presence or absence of foveal lesions in each patient.

Practical points of note were observations that: most patients maintained central visual acuity of 20/60 or better until their middle thirties; an atrophic-appearing foveal lesion was, with 2 exceptions, accompanied by a significant degree of reduction in central acuity; in the absence of an atrophic foveal lesion the majority of patients showed visual acuity of 20/30 or better; there was a trend for more extensive atrophic foveal lesions and more dense lens opacities to occur in older patients, which was not surprising.

Dr Pagon suggests that we may have overlooked what, in her interpretation, is the most useful and reliable predictor of age-related visual loss in the Usher's syndrome, that being the degree of congenital neurosensory hearing loss. There are no data, however, which support her contention. The references which she cites are useful in illustrating the clinical and presumed genetic heterogeneity within Usher's syndrome with which we fully concur. We do not, however, agree that the cited figure, of 90% having profound congenital deafness is an accurate assessment. Our most recent data show that only one-third of 62 patients with Usher's syndrome showed profound neurosensory hearing loss.¹ Most relevant is our observation that the level of hearing impairment was not a good predictor of central visual acuity. There was, as other investigators have noted, a tendency for those with profound neurosensory hearing impairment to manifest an earlier onset of nyctalopia and show earlier and more profound losses in peripheral visual field. We are concerned that erroneous counselling of patients may result if the degree of congenital neurosensory hearing impairment is used as an indicator of future central visual loss.

Finally, we still maintain that a larger sampling of cases over the age of 50 would be helpful to establish the spectrum of visual loss in older age groups more reliably. We join our colleague in her concern for

optimally accurate and meaningful advice for this most unfortunate group of patients.

GERALD FISHMAN
VICTORIA VASQUEZ
MARLENE FISHMAN
DALE BERGER

Reference

¹Fishman GA. Usher's syndrome: visual loss and variations in clinical expressivity. *Perspect Ophthalmol* 1979; 3: 97-103.

Notes

Irish Ophthalmological Society

The Annual Meeting of the Irish Ophthalmological Society will be held in Dublin on 25-26 April 1980. Proceedings on the latter date will be conducted as a joint meeting with the Hellenic Ophthalmological Society. The Montgomery lecture will be given on 26 April by Professor A. Bouzas, of Athens. Visiting ophthalmologists are invited to participate. Inquiries should be addressed to Dr G. P. Crookes, Hon. Secretary, Irish Ophthalmological Society, 18 Fitzwilliam Place, Dublin 2, Ireland.

Ultrasound symposium

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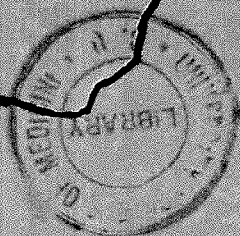
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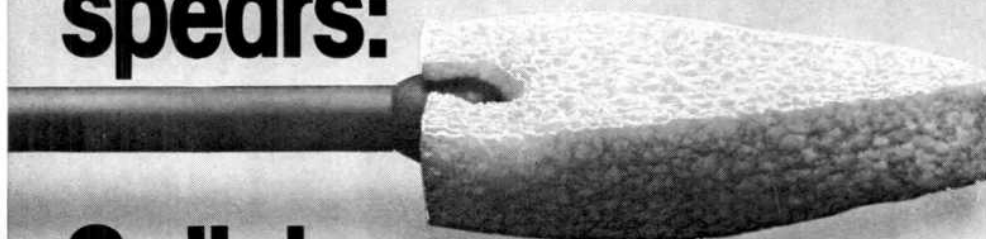
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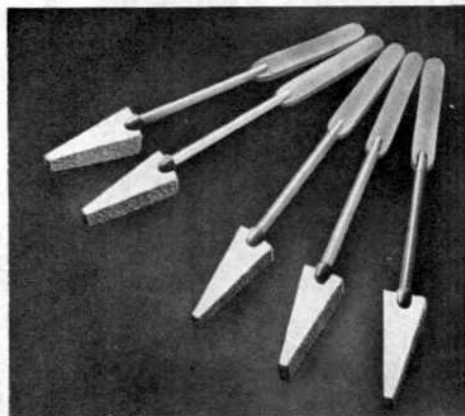


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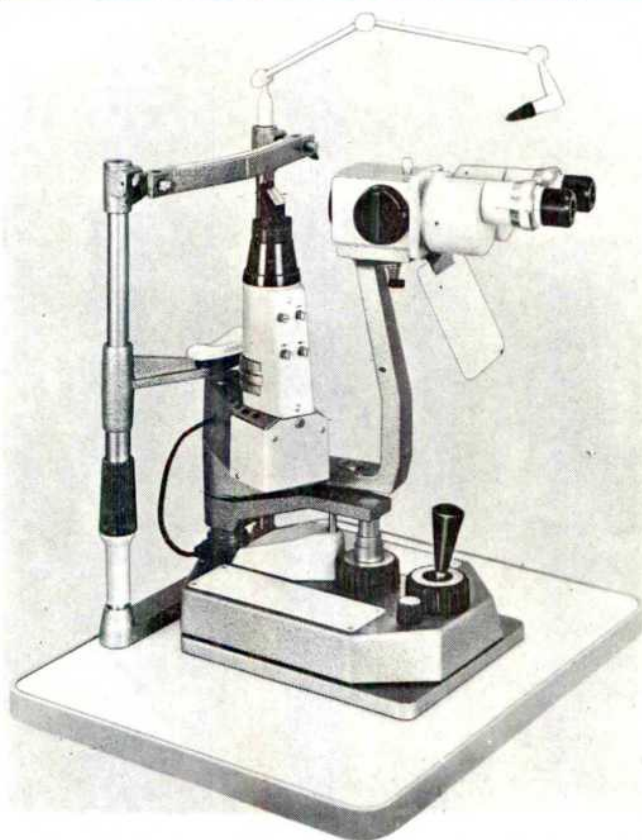
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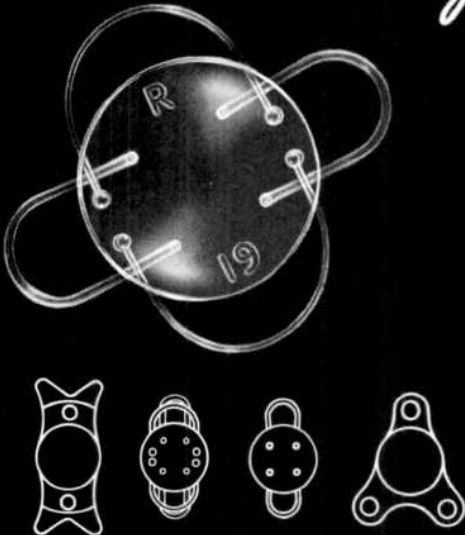
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Drugs and Disease

The Proceedings of a Symposium
organised by the
Royal College of Pathologists

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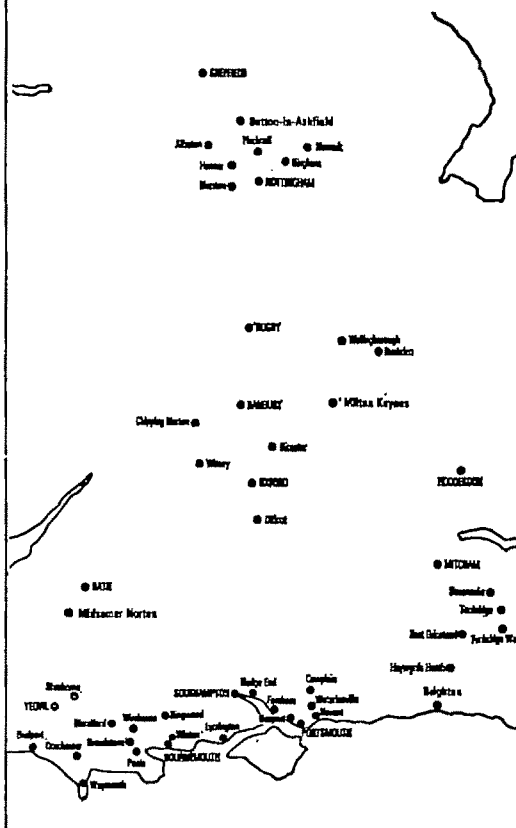
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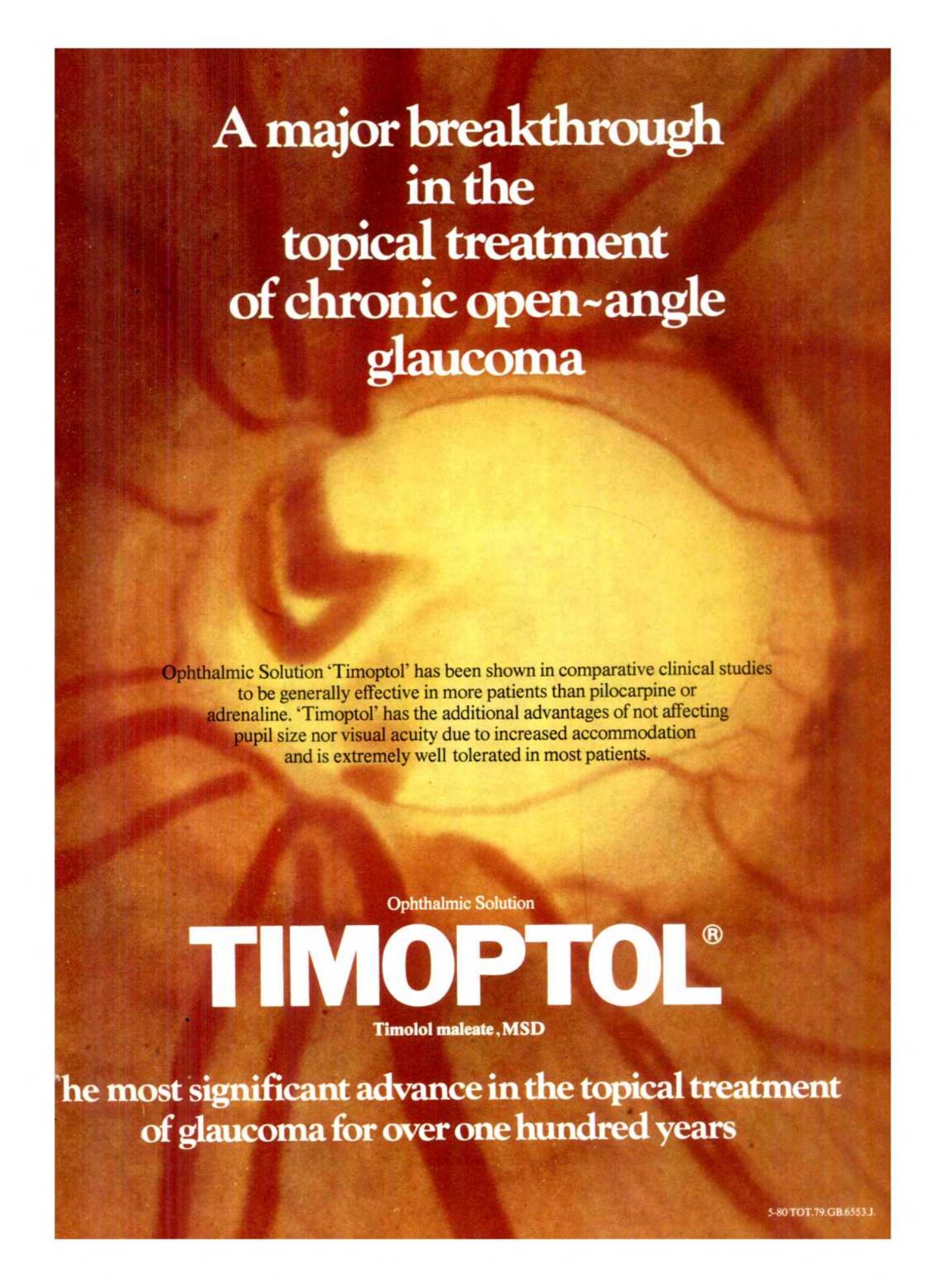
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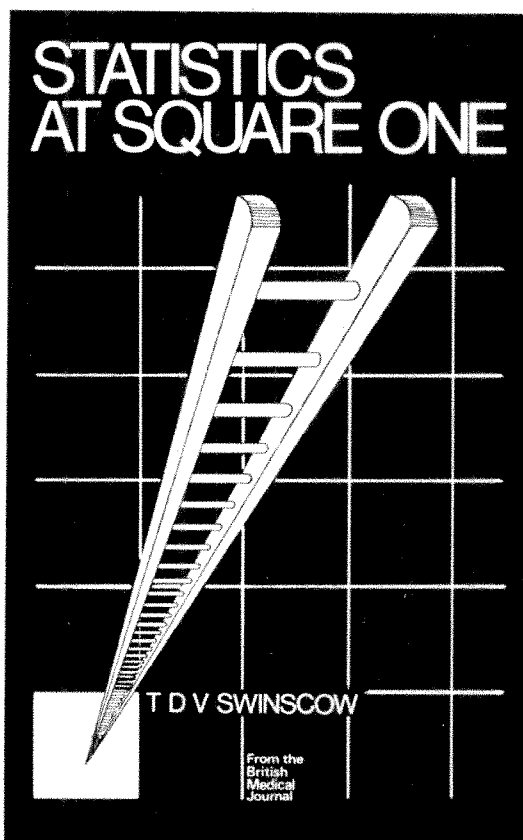
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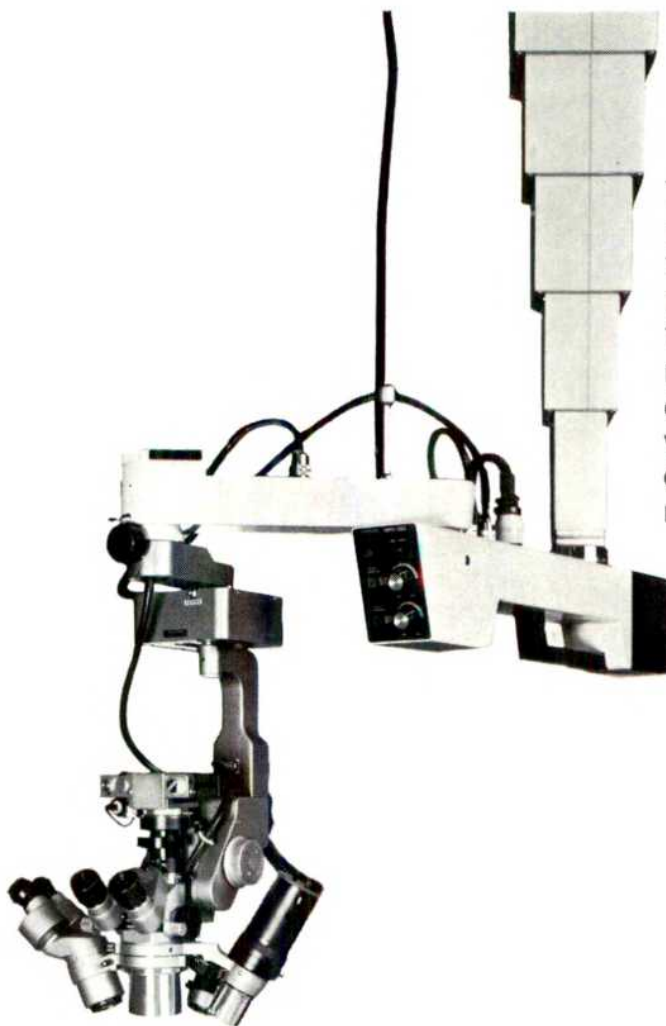


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Editorial: Effect of cyclosporin A on the survival of corneal grafts in rabbits

The substantially improved prognosis for corneal grafts which has resulted from better surgical techniques and applied corneal biology have made the allograft reaction the most important single cause of corneal graft failure and a major obstacle to progress in corneal transplantation. Although allograft reactions are rare in avascular corneas, in grossly diseased vascularised corneas graft rejection is a significant problem. For example, it occurs in over one-half of penetrating grafts performed in eyes with herpes simplex keratitis.

The cornea is unique in that clinical manifestations of graft reactions can be observed easily, and topically administered corticosteroids are frequently effective in preventing and suppressing allograft reactions. However, corticosteroids are by no means always effective, and their use is associated with serious complications—in particular, the development of glaucoma and cataract and the recurrence of ulceration in herpetic eyes. Systemically administered corticosteroids and other immunosuppressive drugs may also cause adverse reactions. Tissue matching, although shown to be effective in corneal transplantation, is of little practical use at present because of major logistical problems.

Cyclosporin A, the subject of an article at page

148, is a new and potent immunosuppressive agent which has aroused considerable interest in the field of transplantation. It has been shown to be effective in preventing allograft reactions in many organs and tissues in a variety of different animals and has been used clinically. It has a marked effect on the allograft response in the rabbit cornea. Its precise mode of action has not yet been determined, but it appears to inhibit the production of antibody by T lymphocytes at the time of exposure to transplanted antigens. Although cyclosporin A lacks the adverse side reactions of other immunosuppressive drugs, it is not without toxic effects, most notably a significant incidence of lymphoma. However, it should be pointed out that lymphoma is a recognised complication of other immunosuppressive regimens.

The fact that cyclosporin A has been shown to inhibit the corneal allograft reaction in rabbits makes it a drug of considerable interest to ophthalmologists, though the present state of knowledge does not justify its use in clinical corneal transplantation. Clearly the effects of topical administration on corneal grafts need to be investigated. In the longer term the significance of cyclosporin A may prove to be that it heralds the advent of a new class of drugs having very specific effects on the allograft response.

Editorial: Early diagnosis of choroidal melanoma

Malignant melanoma of the choroid is the most elusive intraocular tumour. It is notoriously unpredictable and does not follow set rules. In some cases a large tumour may remain localised for a few decades and even undergo spontaneous regression, whereas in others a small lesion of relatively innocent appearance may shower lethal metastases. The latter characteristic is further highlighted in the case study this month of Char *et al.*¹ They report that diffuse choroidal melanomas are particularly treacherous; not only are they difficult to diagnose but they also undergo early extraocular extension. Since the patient's life as well as his sight may be at stake, early detection of such tumours is of paramount importance. It is imperative, however, to differentiate lesions simulating malignant melanoma so that unnecessary enucleation may be avoided. Mistakes in the diagnosis of melanotic lesions are not uncommon. Depending on the experience of the surgeon, the nature of the growth, the availability of reliable diagnostic aids, awareness of simulating lesions, and prevalent attitude towards intraocular malignancy, the incidence of unwarranted enucleation may vary from 3 to 24%.²⁻⁵

Although malignant melanomas of the choroid need to be differentiated mainly from spindle cell naevus, metastatic carcinoma, choroidal haemangioma, and massive subretinal haemorrhage, they may occasionally be confused with posterior scleritis, postoperative choroidal detachment, disciform retinal degeneration, retinal angioma, osseous choristoma of the choroid, and hyperplasia of retinal pigment epithelium. The clinical features and the ophthalmological appearance of such lesions are insufficient for a definitive diagnosis, and therefore several noninvasive diagnostic techniques have been described with intent to avoid unnecessary enucleation as well as to prevent any undue risk to the life of the patient. The following is a short account of the most popular diagnostic methods.

Fluorescein angiography is valuable in detecting acute and chronic changes in the pigment epithelium and the sensory retina overlying a suspected neoplasm. The presence of drusen, choroidal neovascularisation, and cystoid retinal degeneration are suggestive of a slowly growing and probably 'benign' tumour. Malignant melanomas show wide variation in their growth pattern and degree of pigmentation. The angiographic picture is thus a reflection of these variables. In general, however, evidence of widespread destruction or reactive

proliferation of the pigment epithelium with multiple pin-point leakage of dye from the surface of the lesion is indicative of a rapidly growing tumour.⁶ The finding of an irregular pattern of moderate-size blood vessels within a raised choroidal mass suggests a malignant neoplasm. Since benign choroidal naevi are often confined to outer layers of the choroid, they do not usually produce changes in the pigment epithelium and present with hypofluorescent filling defect within a normal pattern of background fluorescence. Angiography alone will not differentiate a metastatic carcinoma from a melanoma, especially if it is amelanotic.

The *radioactive phosphorus* (³²P) test for intraocular melanoma was introduced 28 years ago and has since evoked both staunch opposition and blind faith. The dust of stormy debates has yet to settle, mainly because of the test's unreliability in the diagnosis of small lesions in the posterior pole. Furthermore there does not appear to be a significant correlation between ³²P uptake and the size of the tumour, the cell type, and frequency of mitosis and hence degree of malignancy.

Since recent improvements to the probe and its application after conjunctival incision for posteriorly placed tumours, the reliability of the ³²P test has much improved and appears to be positive in over 90% of patients with malignant melanoma of the choroid.⁷⁻⁹ The test may be negative, however, for small tumours and may be falsely positive for large naevi, haemangioma, leiomyoma of the ciliary body, granulomatous uveitis, hyperplasia of retinal pigment epithelium, and osseous choristoma of the choroid.^{3,6,10} Furthermore the ³²P test cannot differentiate malignant melanoma from metastatic carcinoma of the choroid.

In a study reported in this issue of the journal Moseley and Foulds¹¹ have re-evaluated the ³²P test in the diagnosis of intraocular malignancy. They have carried out this test using a newly developed solid state detector consisting of a beta-sensitive conductor and have found that an 80% increase in radioactive uptake over the control value is strongly indicative of malignancy.

Ultrasonic evaluations in ophthalmology currently use frequencies of 5 to 25 MHz to provide echoes from the physical interfaces between tissues and cells having sufficient acoustic discontinuities to reflect sound. Three display modes are in use; the A mode, B scan, and the M mode. Of these the B scan is the most popular and easy to interpret,

because the 2-dimensional display corresponds to the histological cross-section of the lesion. In combination with the A mode it is of utmost importance in the differential diagnosis of posterior pole lesions, especially when ophthalmoscopic examination cannot be carried out because of opaque or hazy media.¹² A malignant melanoma on the B scan appears as a solid mass with a smooth and generally convex surface, but when it breaks through the Bruch's membrane it gives rise to a collar-stud appearance, which is rare in metastatic carcinoma and is not seen in haemangioma. The measurement of increase in size of a tumour over a period of time will differentiate rapidly growing metastatic carcinoma from a usually slow growing spindle cell melanoma. Ultrasonic evaluations when carried out in conjunction with ³²P test appear to provide the most reliable data for differential diagnosis of a choroidal lesion, and several studies at various centres indicate a 95% reliability for differentiating neoplasms from non-neoplastic lesions.^{8, 12, 13}

Immunological tests for the diagnosis of intraocular melanoma are in their infancy. Although it has been shown that choroidal melanoma cells contain both surface membrane and cytoplasmic tumour-associated antigens,¹⁴ the current methods of detection of cellular and humoral immunity to these antigens suffer from several drawbacks, mainly because the true nature of the tumour antigens is unknown and therefore the interpretations of false positive or negative results are extremely difficult. In an indirect immunofluorescent study of tumour antigenicity¹⁵ cells from malignant melanoma of the choroid were exposed to sera from patients with a variety of non-neoplastic disorders, and it was found that an appreciable proportion of the sera were associated with positive cytoplasmic fluorescence. Further immunological studies,¹⁶ however, showed that a proportion of these antibodies were directed against a contractile element present in a variety of mammalian tissues. In this issue of the journal Malaty *et al.*¹⁷ show conclusively that the cytoplasm of melanoma cells contain actin filaments which are the main source of cross-reactivity and error in immunodiagnosis. Until sensitive methods are developed to remove successfully all the cross-reacting antibodies, the results of serological tests for the diagnosis of choroidal melanoma need to be interpreted with circumspection. Sunba, Rahi and Morgan, in a study (to be reported) of cellular immunity against such tumours, have found a

positive correlation between lymphocyte transformation and extraocular extension of the lesion. Again the technique appears to be unreliable in the early diagnosis of choroidal melanoma, but it promises to be another useful test for determining the prognosis of this elusive and unpredictable tumour.

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Effect of cyclosporin A on the survival of corneal grafts in rabbits

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SUMMARY Cyclosporin A given to rabbits intramuscularly in a dose of 25 mg/kg/day for up to 28 days after corneal transfer results in a marked prolongation in the survival of penetrating corneal grafts compared to that in an untreated control group. Cyclosporin A 1% drops did not prolong survival of the corneal graft, but this may be related to the need for skin transfer 14 days after corneal transfer to ensure rejection, and supports the idea that the drug plays an immunosuppressive role at the time and place of sensitisation.

The fungal metabolite, cyclosporin A, which has potent antilymphocytic activity and little toxicity in mice, rats, rabbits, dogs, and pigs, has been shown to prolong survival of a wide range of allografts in animals and man.¹ It offers an outstanding prospect for effective suppression of the allograft response, a major obstacle to progress in transplantation surgery.

Advances in microsurgery and increasing awareness of the role of the endothelium and the importance of its preservation have highlighted rejection as the major obstacle to successful corneal transplantation. Allografts in vascularised corneas are associated with much higher rates of rejection than those in avascular corneas.² The prognosis for corneal grafts correlates also with immunological parameters such as the degree of histocompatibility³ and the presence of cytotoxic antibodies prior to surgery.³ Tissue matching, although useful in high risk patients, is not a practical solution to the problem at present. The future of corneal grafting in high-risk patients is related to the development of effective immunosuppression without the complications of conventional regimens.

The behaviour of allografts varies considerably with different tissues and from species to species. It is necessary to examine a prospective immunosuppressive treatment in precisely the situation for which it is intended. The purpose of this study has

been to examine the effect of cyclosporin A on the survival of corneal grafts. Penetrating corneal grafts in rabbits provide the opportunity for preliminary investigations.

In contrast to skin and other allografts, in which the mean survival time is short and reproducible, grafts performed into healthy avascular corneas enjoy prolonged survival, and only a very small percentage undergo graft rejection. To ensure rejection of corneal allografts in rabbits, it is necessary to induce vascularisation of the graft and transfer skin to ensure sensitisation.

Materials and methods

The experiments involved the transfer of corneas between rabbits from different breeding stock, followed by exchange of skin grafts between the same pairs 14 days later.

ANIMALS

Pairs of outbred Dutch rabbits (weight 1-2 kg) from 2 different sources (Hyline and Gareside) were used to ensure grafts were exchanged between unrelated animals.

OPERATIVE PROCEDURE

Corneal transfer. 6 mm penetrating grafts were exchanged between pairs.

After induction of anaesthesia full mydriasis was obtained with phenylephrine 10% and atropine 1%. In addition each rabbit received 5000 units of

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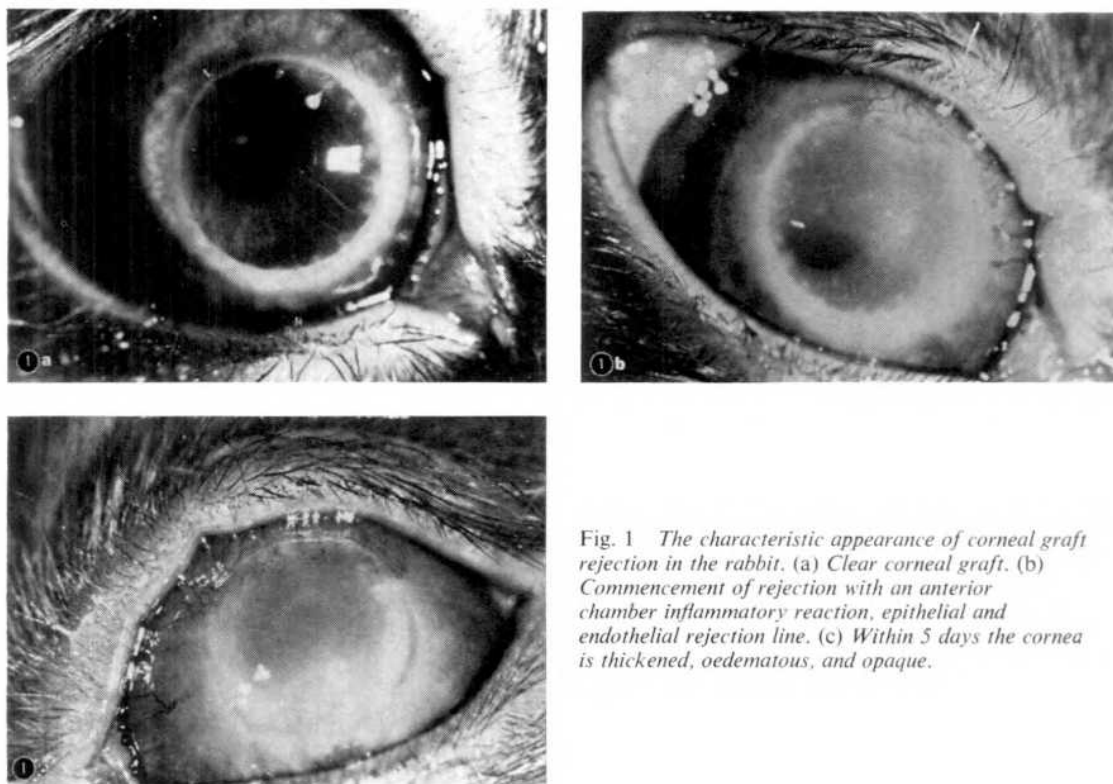


Fig. 1 The characteristic appearance of corneal graft rejection in the rabbit. (a) Clear corneal graft. (b) Commencement of rejection with an anterior chamber inflammatory reaction, epithelial and endothelial rejection line. (c) Within 5 days the cornea is thickened, oedematous, and opaque.

heparin intravenously to prevent aqueous clotting during the operation. The eyelashes were cut and superior and inferior rectus sutures inserted to improve corneal exposure and stabilise the globe. 6 mm discs were trephined, the excision of the disc being completed with corneal scissors. The exchanged discs were fixed with 4 stay sutures of 10/0 monofilament nylon and a continuous 10/0 monofilament nylon suture was inserted. The stay sutures were removed before tightening the continuous suture, the knot of which was left exposed to stimulate vascularisation. The anterior chamber reformed spontaneously, but if any synechiae to the interface were present air was injected via a limbal paracentesis.

Corneal sutures were removed on day 14 at the slit-lamp under topical anaesthesia.

Skin transfer. Circular full-thickness skin grafts of 12 mm diameter were exchanged between pairs 14 days after the corneal graft. Only rabbits with corneal grafts which were clear and uncomplicated received skin grafts and were included in the study. Each graft was soaked in penicillin/streptomycin solution before being sutured in place with eight interrupted 7/0 silk sutures and then covered with an antibiotic spray.

ANAESTHESIA

Corneal and skin grafts were done under general anaesthetic.

Animals were anaesthetised with lignocaine through an indwelling venous catheter to facilitate the maintenance of anaesthesia. This was supplemented by topical anaesthesia (proparacaine 0.5%) for the cornea and by infiltrating the skin with 2% xylocaine and adrenaline 1/80 000 prior to skin grafting.

EVALUATION

Cornea. Mydriasis was maintained for 1 week. The animals were examined daily by slit-lamp biomicroscopy for graft clarity, iritis, and corneal vascularisation and scored accordingly. A diagnosis of corneal graft rejection was made when a previously clear graft in a noninflamed eye developed an inflammatory reaction with or without an epithelial or endothelial rejection line and then progressed to endothelial decompensation and corneal opacification (Fig. 1). The time to rejection was taken as the time from corneal grafting to the initiation of these events.

Skin. The progress of the skin graft was examined daily, and the softness, pliability, colour, and

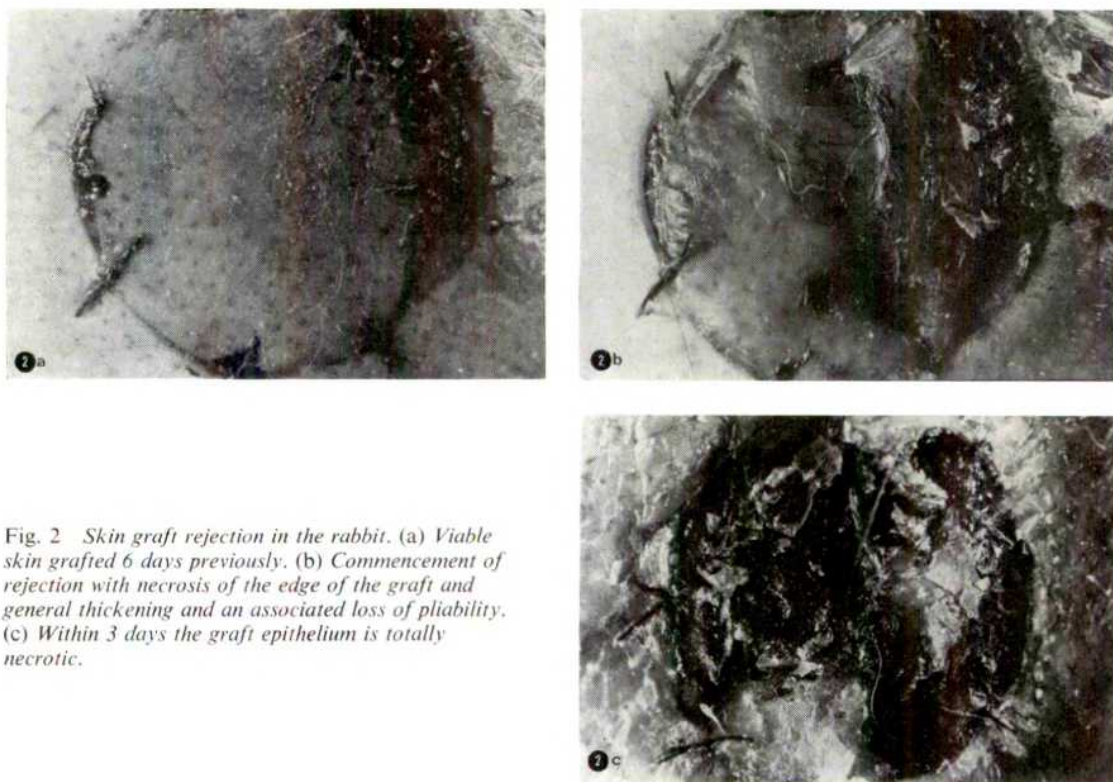


Fig. 2 Skin graft rejection in the rabbit. (a) Viable skin grafted 6 days previously. (b) Commencement of rejection with necrosis of the edge of the graft and general thickening and an associated loss of pliability. (c) Within 3 days the graft epithelium is totally necrotic.

viability were recorded. The time to rejection was taken as the time from skin grafting to the point at which 50% of the previously viable epithelium was necrosed (Fig. 2).

TREATMENT

Animals were allocated to 1 of 5 treatment groups; 1 was a control group, 3 received intramuscular cyclosporin A, and 1 received cyclosporin A in drop form. The details of the treatment schedules are displayed in Table 1. Animals receiving intramuscular cyclosporin A were given 25 mg/kg per

day. Drops were prepared as 1% solution in arachis oil and were given 5 times a day for 28 days.

Results

The results are displayed in Figs. 3–7.

GROUP I

All the animals in the control group rejected their grafts promptly. No corneal rejection was observed prior to skin transfer, but 50% were rejected within 3 weeks of skin transfer, that is, 5 weeks after corneal surgery. One cornea survived 10 weeks after corneal transfer before being rejected, but this was in an eye which had failed to vascularise.

Skin rejection in this control group occurred early. More than 50% were rejected within a week of skin transfer, and all rabbits rejected skin within 2 weeks.

GROUP II

Animals treated with cyclosporin A 25 mg/kg per day intramuscularly for 28 days from the time of corneal grafting showed prolonged graft survival. The extent of this prolongation of corneal survival

Table 1 *Experimental groups*

	Number of animals	Treatment schedule	
Group I	10	Nil—control	
Group II	10	Cyclosporin A 25 mg/kg/day	Day 0–day 28
Group III	8	..	Day 0–day 14
Group IV	11	..	Day 14–day 28
Group V	7	Cyclosporin A 1% eye drops 5 times per day	Day 0–day 28

compared to the control group is set out in Fig. 3, and the prolonged survival of skin grafts is displayed in Fig. 4.

Corneal graft survival was prolonged to the extent that 50% of grafts remained clear 14 weeks after corneal transfer, and 1 graft survived indefinitely. Skin graft survival was also prolonged with 50% of grafts surviving 3 weeks after skin transfer, with 1 graft surviving indefinitely.

GROUP III

A shorter period of administration of cyclosporin A for 14 days from the day of corneal transfer also resulted in prolonged corneal graft survival. 50%

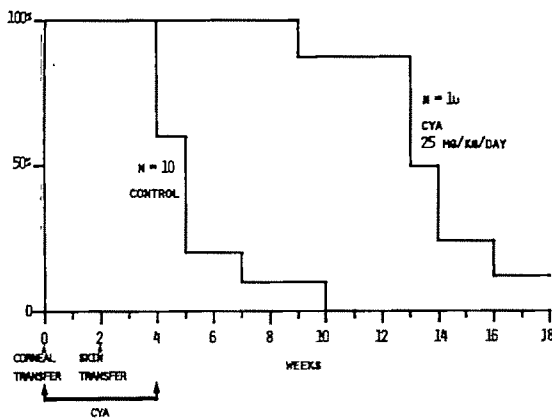


Fig. 3 Survival graph comparing the effect on corneal graft survival of cyclosporin A, 25 mg/kg/day, intramuscularly for 28 days from the time of corneal transfer.

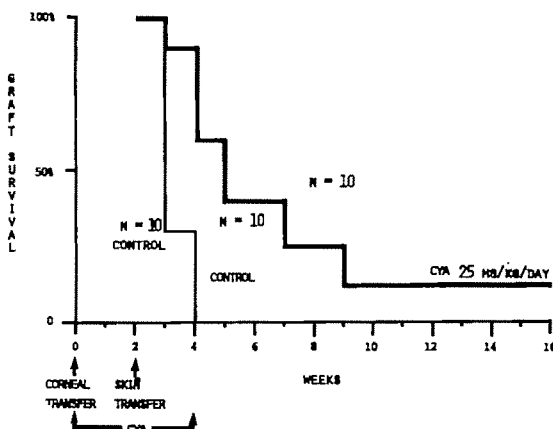


Fig. 4 Survival graph comparing the effect on skin graft survival of cyclosporin A, 25 mg/kg/day, intramuscularly for 28 days from the time of corneal transfer.

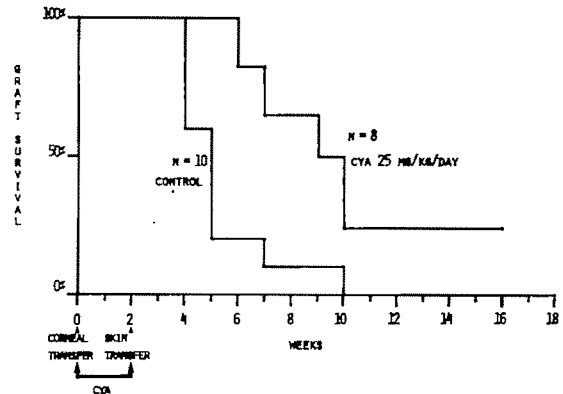


Fig. 5 Survival graph comparing the effect on corneal graft survival of cyclosporin A, 25 mg/kg/day, intramuscularly for 14 days from the time of corneal transfer.

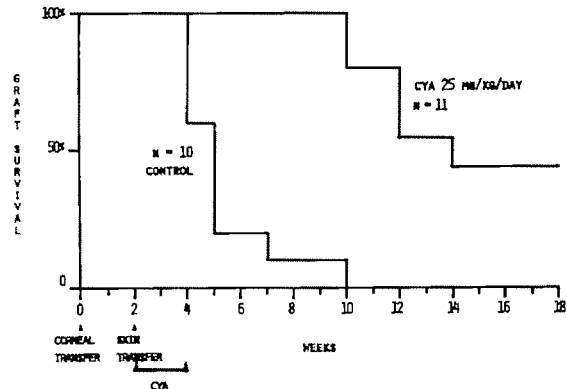


Fig. 6 Survival graph comparing the effect on corneal graft survival of cyclosporin A, 25 mg/kg/day, intramuscularly for 14 days from the time of skin transfer, that is, commencing 14 days after corneal transfer.

of grafts survived 10 weeks, and there were 2 indefinite survivors (Fig. 5).

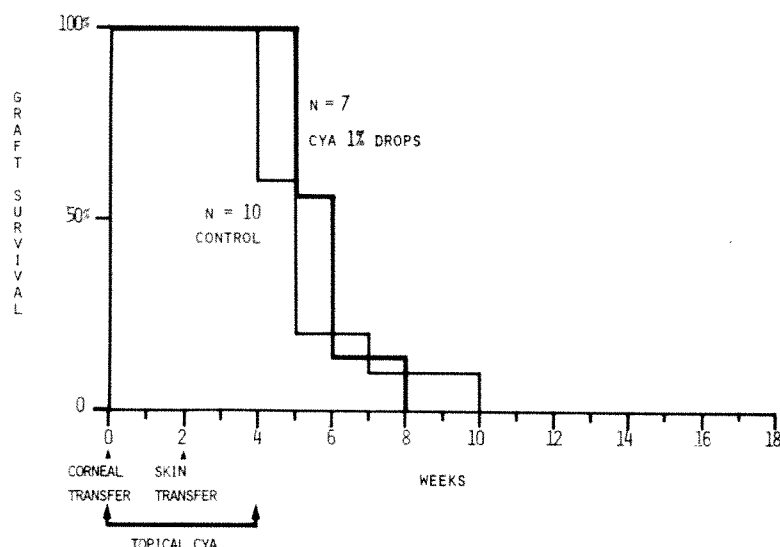
GROUP IV

The administration of cyclosporin A for 14 days after skin transfer was also associated with prolonged corneal graft survival. 50% of corneas remained clear for 14 weeks after corneal transfer. There were 3 indefinite survivors (Fig. 6).

GROUP V

Topical cyclosporin A 1.0% eye drops given 5 times a day for 28 days from the day of corneal transfer did not influence the survival of corneal grafts (Fig. 7).

Fig. 7 Survival graph comparing the effect on corneal graft survival of cyclosporin A, 1.0% eye drops, given 5 times a day for 28 days from the time of corneal transfer.



Discussion

Parenteral cyclosporin A markedly prolongs the survival of corneal grafts in rabbits. These experiments demonstrate several features of this drug, in particular the way in which allograft survival is increased after only short-term therapy and the way in which a proportion of grafts remain unrejected for a very long time.

The results are in accord with those of other workers using different animals and grafting a wide range of tissues. Survival of bone marrow, kidney, liver, and heart grafts in rats, rabbits, pigs, and dogs as well as heart grafts in nonhuman primates⁴⁻¹² have been markedly prolonged and encourage the use of cyclosporin A in clinical practice. Clinical experience so far is restricted to a small number of centres involved in essential organ grafting. In terms of graft survival and prevention of graft-versus-host disease in bone marrow recipients, the clinical use of this drug has been most encouraging.^{13,14} Two major difficulties have arisen. Although cyclosporin A is not myelotoxic to any degree, changes do occur in the liver and kidney related to its administration, but what is more worrying is the high incidence of lymphoma in the small number of patients receiving the drug.¹

No substantial degree of systemic toxicity is justifiable with a drug used to protect grafts in nonessential organs such as the cornea. Since it is unlikely that immunosuppression without complications can be achieved with a systemic drug, the future of corneal grafting is very much related to the development of immunosuppressive agents that can be effectively delivered topically.

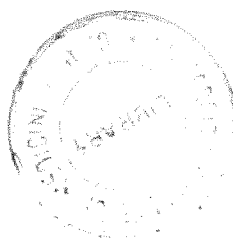
Failure of topically applied cyclosporin A in these experiments may be related to the model. It has been clearly shown that cyclosporin A is more likely to be effective when it is delivered with an antigen. Failure of the drug when it is applied directly to the eye is not surprising in a model in which remote skin grafts provide the sensitisation necessary to initiate corneal graft rejection. An encouraging feature was the way in which the rabbits tolerated the topical preparation; there was no untoward reaction apparent in the cornea or conjunctiva, but there was an initial loss of hair from the eyelids. Clearly different models are needed to assess the potential for topical treatment of this drug, and these studies are being pursued. The unique specificity and low toxicity of cyclosporin A suggest that this class of drug is more likely to offer a solution to the problem of corneal graft rejection than any agent yet tested.

We thank Dr J. F. Borel of Sandoz Ltd., Basle, for supplying the cyclosporin A and for his invaluable advice.

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Aetiology of climatic droplet keratopathy and pterygium

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SUMMARY The association of various personal, occupational, and environmental factors with climatic droplet keratopathy and pterygium was examined in a group of Australian Aborigines. Climatic droplet keratopathy was seen especially in aboriginal males who had worked as stockmen for more than 20 years. Although no definite association with a single causal factor could be made, there is circumstantial evidence for the importance of ultraviolet radiation. Pterygium was more commonly seen in those who worked outside, and it was positively correlated with lower latitudes and high ultraviolet levels.

In 1965 Freedman¹ described a bilateral acquired corneal degeneration occurring in indigenous populations in Labrador and Northern Newfoundland, which he called Labrador keratopathy. This keratopathy was characterised initially by the presence of small droplets at the level of Bowman's membrane, and these progressed to give a haze and eventually were sometimes associated with the development of yellow nodules.

This keratopathy resembles that described by Zanettia,² Falcone,³ and Bietti *et al.*⁴ in the Dahlak Islands in the Red Sea, Somalia, Eritrea, and Saudi Arabia. The keratopathy seen in the Dahlak Islands was examined further by Rodger.⁵ He found that although the keratopathy showed the same course of progression with age as was seen in Labrador, more people were found with the disease's advanced stage that included the opacification of the whole stroma and sloughing of nodules.

Since then Fraunfelder and his associates have described a condition that they have called 'spheroidal degeneration' of the cornea and conjunctiva.⁶⁻⁹ This condition is characterised by small golden or yellow globules. It may be a primary condition of an otherwise normal cornea or conjunctiva, or it may be secondary to other ocular pathology, especially absolute glaucoma, trauma, or pterygia. Garner *et al.*¹⁰ reported these golden droplets in 6% of patients presenting to an eye clinic in England.

Many have considered that the 2 conditions are the same environmentally induced corneal degeneration.

It would appear, however, that 2 different conditions are being described. The condition that Freedman and Rodger described appears to be related to severe climatic conditions and starts as a fine frosting of clear vesicles at the level of Bowman's membrane. It is more severe in the Red Sea littoral, where it may progress to total stromal involvement and scarring. The second condition, described by Fraunfelder and associates, is a milder degenerative condition characterised by golden globules. It is more often seen as a mild ageing process in otherwise normal eyes, or it may develop secondarily to severe corneal disease, ocular trauma, or glaucoma, or even as a secondary phenomenon in the degeneration described by Rodger and Freedman. That these conditions may be different has been alluded to by Johnson and Ghosh¹¹ and by Anderson and Fuglsang.¹² It is therefore proposed to differentiate between the 2 conditions, and (1) to refer to the specific condition described by Freedman and Rodger as 'climatic droplet keratopathy' (Labrador keratopathy), as suggested by Freedman^{13,14}; and (2) to use Fraunfelder's terminology of 'spheroidal droplet degeneration' for the condition that in some cases may be an ageing phenomenon and sometimes may be secondary to other corneal pathology. It is not proposed, however, to enter further into the argument about nomenclature of these conditions.

The aetiology of climatic droplet keratopathy is

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unknown. An environmental cause has been proposed for this condition from the time it was first described.¹⁻⁵ An environmental cause is thought likely because the keratopathy has a relatively uniform clinical appearance and a striking regional distribution. Attention has been drawn in particular to ultraviolet light, as all the areas in which this keratopathy has been found have high levels of ultraviolet light.

In northern Canada and in the other areas studied by Forsius,¹⁵ an inverse relation was found between the prevalence of climatic droplet keratopathy and the degree of shelter from sunlight provided by trees. This variation with shelter from the sun was also noted by Anderson and Fuglsang¹² in West Africa. Rodger *et al.*¹⁶ measured the amount of ultraviolet light present in the Dahlak Islands and found it to be 6 to 7 times greater than in England.

Bietti *et al.*⁴ suggested that drying of the cornea may be the initiating factor, because the patients he saw lived in hot arid conditions. Although the arctic regions of Canada are by no means hot, they share with the desert a very low humidity, which in the arctic approaches zero level in winter. Wind is also a factor that may affect corneal drying and can lead to particulate injury from dust or driven snow, and such trauma has been implicated as an aetiological factor. As each of these latter factors (low humidity and windborne microtrauma) is also less severe in wooded areas, the case for ultraviolet light as the causative agent—which is based on regional variation—becomes less strong. It is of interest that those who have looked at the tear film have not found any abnormalities.^{4, 5, 13, 14, 17, 18}

The finding of cases in South Africa¹⁹ and in south-eastern USA²⁰ would, however, support the theory of ultraviolet light, which is at present the most widely held. Therefore the conditions most likely to lead to the development of this keratopathy would appear to be aridity, intense sunshine, and windborne particles. The relative importance of sunshine or ultraviolet radiation has not been examined fully.

Ringland Anderson²¹ was the first to try to relate the geographical distribution of pterygium to local meteorological factors. His data, which covered most of Australia, dealt with the prevalence of surgery for the removal of pterygium. He concluded that the most likely factor influencing the frequency of pterygium was corneal drying.

Others have also suggested that pterygia occur as the result of disruption of the tear film either by rapid evaporation or microtrauma from micro-particles of dust.²²⁻²⁵ Cass (personal communication) also suggested that irritation from fires and

dust is important. However, no tear film abnormalities have been found in people with pterygia.^{19, 26}

Cameron,²⁷ in his monograph on pterygium, considered the world distribution of this condition. He found that although countries that are hot, dry, and dusty had a higher prevalence of pterygium, there were other areas that, although hot, were neither dry nor dusty and yet also had a high prevalence of pterygium. The common factor appeared to be latitude, and he related this to ultraviolet irradiation, which varies with latitude. He postulated that ultraviolet light damages Bowman's membrane and causes a thickening and hyperplasia in the subconjunctival connective tissues, and that these combined changes result in pterygium. While the probable role of ultraviolet light in the initiation of pterygium is now generally accepted, there has been no direct evidence linking ultraviolet light and pterygium.

The following study investigated the role of a number of personal and environmental factors in the causation of these 2 conditions. This study was conducted as a separate study in conjunction with the routine field work performed by the National Trachoma and Eye Health Programme (NTEHP).

Patients and methods

The Aborigines examined in this study came from one of 2 groups. Firstly, any Aborigine whose best corrected acuity was 6/60 or less in either eye was included in the study together with the next Aborigine to be seen who was of the same sex, whose age was in the same decade, and who had corrected vision of 6/12 or better in both eyes.²⁸ 312 people were included in these groups. Secondly, 82 Aborigines were selected by examining 50% of the Aborigines over the age of 30 in two aboriginal communities. The sample was drawn randomly after the population had been enumerated.²⁹ In some cases these 2 groups overlapped in that some of those in the prevalence study (the second group) were also included in the study of blindness (the first group). A total of 350 Aborigines over the age of 30 are included in this study.

HISTORY

A detailed history including age, sex, tribe, and the type and duration of any previous occupation was obtained, together with details of where the patient had spent most of his or her life (residence). A history of both alcohol consumption and ocular trauma was also sought. In every case the questions were asked in a standard order and in the same way. A methodology trial showed that these questions were answered consistently.²⁸

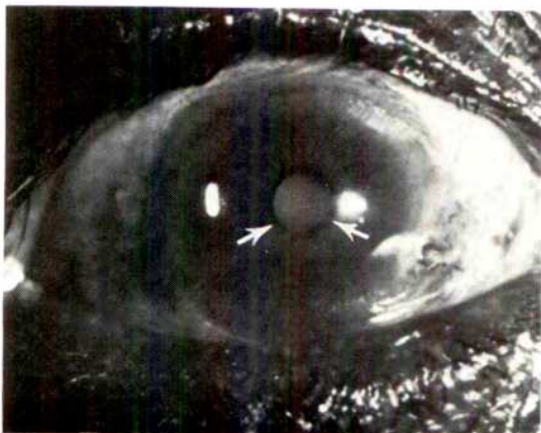


Fig. 1 Grade 2 climatic droplet keratopathy. Fine droplets lying at the level of Bowman's membrane in the area of the interpalpebral fissure extend over the central cornea. Their presence is shown by the blurring of the underlying iris details and of the pupillary margin (between arrows).

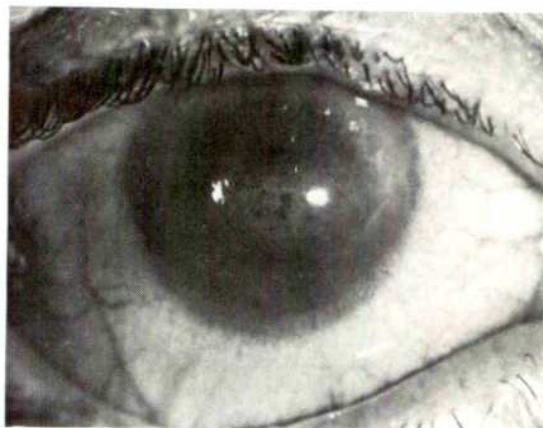


Fig. 2 Grade 3 climatic droplet keratopathy with a dense accumulation of droplets and reduction of visual acuity. Clear areas of lacunae are seen centrally.

EXAMINATION

Visual acuity was tested with a standard chart, usually an illiterate E chart. Best corrected vision was recorded. Each patient was examined for signs of trachoma with a loupe and suitable illumination. Trachoma was graded according to the severity of 7 signs according to the NTEHP grading protocol.²⁸ After the grading for trachoma, all people were examined with a slit-lamp and with direct and indirect ophthalmoscope.

CDK was graded as follows: grade 1, peripheral changes present; grade 2, changes across the pupillary axis; grade 3, changes leading to a decrease in visual acuity; grade 4, the presence of nodules (Figs. 1–3).¹¹ The extent of pterygia was recorded in millimetres.

ANALYSIS

To facilitate statistical comparison of the presence and severity of trachoma an index called 'Trachoma Scarring Index' was used.²⁸ This index draws on the severity of the individual signs of structural change or cicatrization caused by trachoma, but lends more weight to the presence of multiple abnormalities. Individuals are classified by their worse eye.

Meteorological data were obtained from publications of the Bureau of Meteorology.^{30–32} These parameters were then recorded for the location where each patient had spent most of his or her life (residence). The mean daily maximum temperature, the mean daily relative humidity at 1500 h, the evaporation rate, and the average daily global

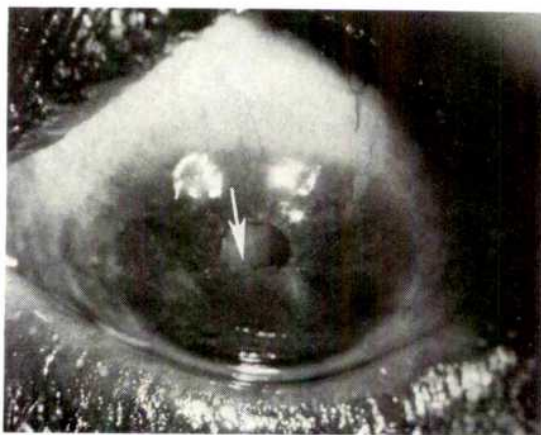


Fig. 3 Grade 4 climatic droplet keratopathy with extensive fine droplets covering the exposed cornea. Larger golden yellow droplets are seen immediately above this band overlying the pupil (arrow). This eye also has extensive trachomatous pannus and Herbert's pits, nuclear sclerosis, pseudoxfoliation, and a small pterygium which is not well shown.

radiation were recorded for the month of January and for the year. The average daily hours of sunlight and the median annual rainfall were also recorded. The amount of ultraviolet B radiation for each location was determined from maps prepared by calculation, with verification using observed data.³³ The latitude, longitude, and altitude of each place of residence were also recorded.

The data were coded on specially prepared clinical sheets and transferred to computer tape. A detailed analysis of possible associations between the personal, environmental, and general variables

Climatic Droplet Keratopathy Associated with:

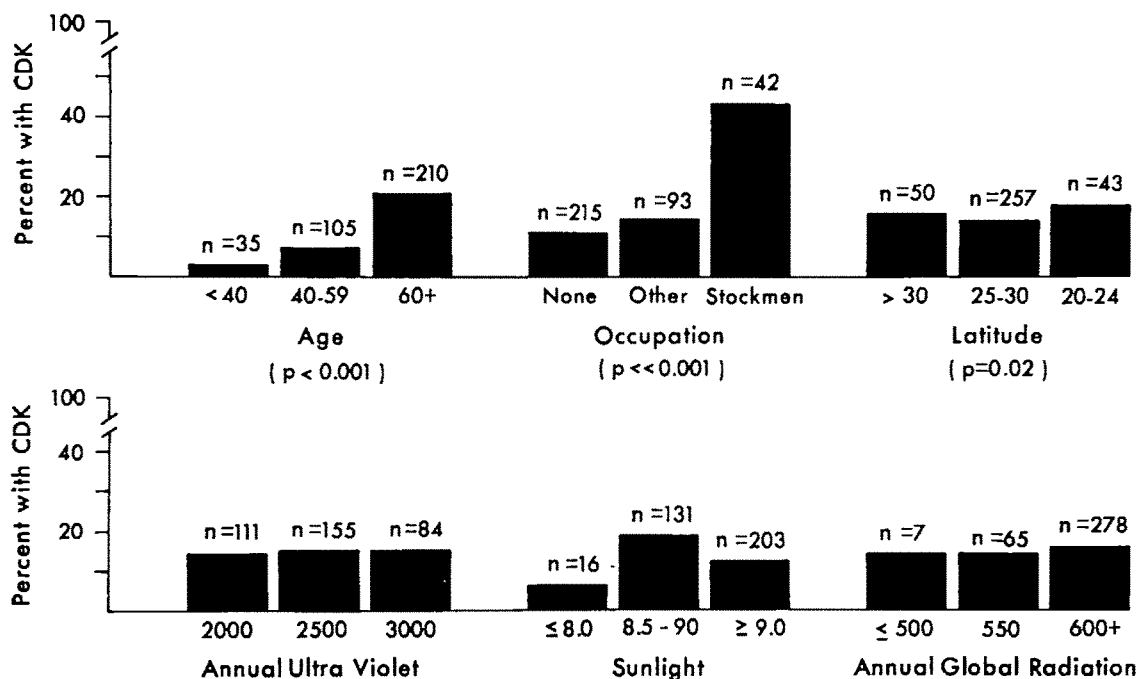


Fig. 4 Histograms showing the prevalence of climatic droplet keratopathy in 350 Aborigines by age (years), occupation, latitude (degrees), annual mean ultraviolet B radiation (minimal erythema doses), annual mean daily hours of sunlight, and annual mean daily total global radiation (mW/h/cm²).

and the presence or absence of CDK and pterygium was conducted on the Unix time-sharing PDP 11/45 computer at the Johns Hopkins Hospital. The test of statistical significance used throughout was the chi-square test. For simplicity only the P values are presented, but it must be remembered that the associations of many variables were examined.

Results

CLIMATIC DROPLET KERATOPATHY

In the 350 individuals examined 52 people (43 males and 9 females) with CDK were seen. The sex correlation was very significant ($P < 0.001$). CDK was found more often in the elderly (Table 1, Fig. 4). CDK was strongly related to a history of occupation as a stockman ($P < 0.001$) (Table 1, Fig. 4). However, no difference was seen in the frequency of CDK between the other groups of outdoor workers, and people with other jobs, and those who had not worked. Among the stockmen a strong correlation was seen between CDK and the length

Table 1 Distribution of climatic droplet keratopathy by age and occupation in 350 Aborigines*

	Climatic droplet keratopathy		
	Present	Absent	Total
Age (years)			
0-39	1	34	35
40-59	7	98	105
60 or more	44	166	210
Occupation			
None	23	192	215
Stockman	18	24	42
Station hand	5	33	38
Labourer	2	8	10
Other	4	41	45
Total	52	298	350

* χ^2 test: Age $P < 0.001$; occupation (stockmen vs. rest) $P < 0.001$.

of time worked as a stockman. None of 8 who had worked as stockmen for less than 20 years had CDK, whereas 16 of 34 who had done that work more than 20 years had CDK ($P=0.006$).

No relation existed between the severity of trachoma and the presence of CDK. No relation was found between CDK and latitude (Table 2). Stockmen are analysed separately, as the prevalence of CDK was high in this group. CDK was seen more often in areas with 9 or more hours of sun-

Table 2 *Distribution of climatic droplet keratopathy by latitude and mean daily hours of sunshine for the group as a whole and for the 42 stockmen**

	CDK—Whole group			CDK—stockmen		
	Present	Absent	Total	Present	Absent	Total
<i>Latitude (degree)</i>						
20–24	8	35	43	3	3	6
25–30	36	221	257	11	19	30
30 or more	8	42	50	4	2	6
<i>Sunshine (hours)</i>						
8.5 or less	17	61	78	7	8	15
9.0 or more	35	237	272	11	16	27
Total	52	298	350	18	24	42

* χ^2 test: Sunshine whole group; $P=0.05$; stockmen; not significant.

Table 3 *Distribution of climatic droplet keratopathy by mean daily total radiation for January ($mW/h/cm^2$) and ultraviolet radiation (mean erythemal doses) for the group as a whole and for the 42 stockmen*

	CDK—Whole group			CDK—Stockmen		
	Present	Absent	Total	Present	Absent	Total
<i>Global radiation</i>						
800 or less	31	118	149	12	6	18
more than 800	21	180	201	6	18	24
<i>UV dosage</i>						
<i>January</i>						
4000 or less	32	177	209	13	17	30
4500 or more	20	121	141	5	7	12
<i>Year</i>						
2000 or less	15	96	111	5	5	10
2500	24	131	155	7	9	16
3000 or more	13	71	84	6	10	16
Total	52	298	350	18	24	42

Table 4 *Distribution of climatic droplet keratopathy by mean daily maximum temperature for January and mean annual rainfall for the group as a whole and for the 42 stockmen**

	CDK—Whole group			CDK—Stockmen		
	Present	Absent	Total	Present	Absent	Total
<i>Temperature ($^{\circ}C$)</i>						
37 or less	38	166	204	14	11	25
38 or more	14	132	146	4	13	17
<i>Annual rainfall (mm)</i>						
200 or less	15	114	129	6	7	13
200–250	25	148	173	9	16	25
250 or more	12	36	48	3	1	4
Total	52	298	350	18	24	42

* χ^2 test: Temperature—whole group, $P=0.02$; stockmen, $P=0.04$. Rainfall—whole group, $P=0.08$; stockmen, $P=0.08$.

shine per day (annual mean daily hours of sunshine) than in areas with $8\frac{1}{2}$ or less hours of sunshine per day (Table 2, Fig. 4). This correlation was significant for the group as a whole ($P=0.05$) but not significant for stockmen.

Annual total global radiation was not related to the presence of CDK (Table 3, Fig. 4). There was no significant correlation with levels of ultraviolet radiation, either for January or for the year (Table 3, Fig. 4). This was true for both the group as a whole and for stockmen.

A trend existed for CDK to be found more commonly in areas with lower maximum temperatures in January ($37^{\circ}C$ or less) than in areas with maximums of $38^{\circ}C$ and higher (Table 4), though no such trend was seen with annual mean temperatures. No significant correlation existed between CDK and annual rainfall (Table 4), although CDK tended to occur more often in areas with higher rainfall ($P=0.08$ for both groups).

The annual evaporation rate was not correlated with the presence of CDK in the group as a whole, but among stockmen CDK was more commonly seen in areas with lower annual evaporation rates ($P=0.04$). For both stockmen and the group as a whole CDK was seen more often in areas with lower January evaporation rates (Table 5). A high relative humidity in January was associated with a higher incidence of CDK. A similar but not significant trend existed in relation to annual humidity.

When those men who had worked as stockmen for more than 20 years were examined as a separate group, no causative differences were found between those with and without CDK. In all, there were 34 men in this group, 18 with CDK and 16 without.

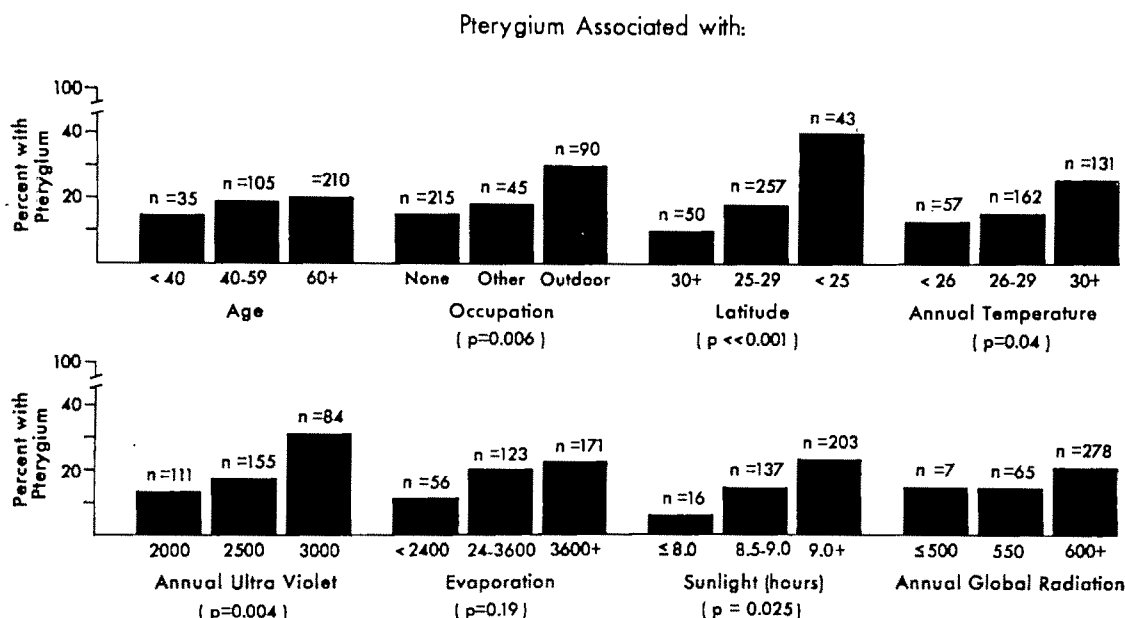


Fig. 5 Histograms showing the prevalence of pterygium in 350 Aborigines by age (years), occupation, latitude (degrees), annual mean daily maximum temperature ($^{\circ}\text{C}$), annual mean ultraviolet B radiation (minimal erythema doses), annual mean evaporation rates (mm), annual mean daily hours of sunlight, and annual mean daily total global radiation ($\text{mW}/\text{h}/\text{cm}^2$).

It may be that the small numbers in these groups obscured any trends or associations that may have been present. There was no tribal bias in the distribution of CDK, nor was there a clustering in relation to places of examination. The factors examined were: age, latitude, altitude, alcohol intake, ocular trauma, and the annual and January values for

ultraviolet radiation, maximum temperature, rainfall, sunshine, global radiation, evaporation rate, and relative humidity.

PTERYGIUM

Sixty-seven people with pterygium were seen; there were 31 males and 36 females. There was no sex correlation nor was pterygium more common with increasing age (Table 6, Fig. 5). Such trends may have been masked by the matching used in the case control study. Pterygium was associated with certain occupations (Table 6, Fig. 5). It was seen more commonly in the 3 groups of outdoor workers (stockmen, station hands, and labourers) than in those with other occupations or those who had not worked. No significant difference existed between the 3 outdoor groups.

A history of alcohol intake, previous ocular trauma, and the severity of trachoma, was not related to the presence of pterygium.

A significant association was found between latitude and pterygium (Table 7, Fig. 5). Pterygia were seen more often in those from lower latitudes ($P < 0.001$). Pterygium was also associated with longer hours of sunlight (Table 7, Fig. 5) ($P = 0.025$) and high levels of total global radiation in January (Table 8, Fig. 5) ($P = 0.04$), but it was not associated with the annual global radiation levels.

Table 5 Relation between climatic droplet keratopathy and total evaporation for January and relative humidity for January for the whole group and for the 42 stockmen*

	CDK—Whole group			CDK—Stockmen		
	Present	Absent	Total	Present	Absent	Total
Evaporation (mm)						
250–500	39	152	191	14	10	24
550–600	13	146	159	4	14	18
Relative humidity (percentage)						
30 or less	18	162	180	4	16	20
30–40	17	66	83	7	4	11
40 or more	17	70	87	7	4	11
Total	52	298	350	18	24	42

* χ^2 test: Evaporation, whole group, $P = 0.001$; stockmen, $P = 0.02$. Humidity, whole group, $P = 0.03$; stockmen, $P = 0.02$.

Table 6 *Distribution of pterygium by age and occupation in 350 Aborigines**

	Pterygium		Total
	Present	Absent	
<i>Age (years)</i>			
0-39	5	30	35
40-59	20	85	105
60 or more	42	168	210
<i>Occupation</i>			
None	32	183	215
Stockman	10	32	42
Station hand	12	26	38
Labourer	5	5	10
Other	8	37	45
Total	67	283	350

* χ^2 test: occupation, outdoor workers vs. rest, $P=0.006$; 4 degrees of freedom, $P=0.01$.

Table 7 *Distribution of pterygium by latitude, annual mean ultraviolet B radiation (mean erythemal doses), and annual mean daily hours of sunshine in 350 Aborigines**

	Pterygium		Total
	Present	Absent	
<i>Latitude (degrees)</i>			
24 or less	17	26	43
25-29	45	212	257
30 or more	5	45	50
<i>Sunshine (hours)</i>			
9.0 or less	20	127	147
9.5 or more	47	156	203
<i>UV dosage</i>			
2000	14	97	111
2500	27	128	155
3000	26	58	84
Total	67	283	350

* χ^2 test: Latitude, $P<0.001$; sunshine, $P=0.025$; UV, $P=0.004$.

A significant association existed between the presence of pterygium and annual mean ultraviolet radiation levels (Table 7, Fig. 5) ($P=0.004$). When those over the age of 40 were examined, the relation between ultraviolet radiation and pterygium was increased ($P=0.001$), but the ultraviolet radiation in the month of January was not significantly related to the presence of pterygium in either age group.

A significant relation was also seen between pterygium and a higher mean annual maximum temperature (Table 9, Fig. 5), and a trend with

higher temperatures in January ($P=0.125$). This may suggest that a continually hot climate is more important in pterygia formation than the extremes of temperature. Pterygia were not associated with the annual rainfall, or the evaporation rate in January. However, pterygium tended to be more common in areas of high annual evaporation rates; those areas with evaporation rates of 2200 mm or less had fewer pterygia than those with evaporation rates of 2400 mm or more (Table 9). A trend also existed for pterygium to be seen less often in areas with an annual relative humidity in the range of 40-59% than in areas with a higher or lower annual relative humidity (Table 9).

Table 8 *Relation between pterygium and mean daily total global radiation (mW/h/cm²) for January and for the year in 350 Aborigines**

	Pterygium		Total
	Present	Absent	
<i>Global radiation</i>			
<i>January</i>			
less than 800	21	128	149
800 or more	46	155	201
<i>Annual</i>			
less than 550	10	62	72
550 or more	57	221	278
Total	67	283	350

* χ^2 test: $P=0.04$ (January); annual, not significant.

Table 9 *Relation between pterygium and annual mean temperature, annual mean daily evaporation rate, and also annual mean relative humidity in 350 Aborigines**

	Pterygium		Total
	Present	Absent	
<i>Temperature (°C)</i>			
25 or less	7	50	57
26-29	26	136	162
30 or more	34	97	131
<i>Evaporation</i>			
2200 or less	6	50	56
2400-3200	24	99	123
3600 or more	37	134	171
<i>Humidity</i>			
40 or less	33	112	145
40-49	16	109	125
50 or more	18	62	80
Total	67	283	350

* χ^2 test: Temperature, $P=0.004$; evaporation, $P=0.19$; humidity, $P=0.08$.

Discussion

Because of the methods used to obtain the groups for this study, no inference can be drawn about the prevalence of CDK or pterygium in the population studied, although an investigation into the role that personal and environmental factors play in causation of these 2 conditions is valid.²⁰

Good descriptions of the clinical appearance of CDK have been given by Freedman,¹³ Anderson and Fuglsang,¹² and Johnson and Ghosh.¹¹ The changes seen in Aborigines were as described by these authors.

Only a few detailed studies of the prevalence of CDK have been reported.^{15 20 24 25} While there are some differences in the distribution and severity of CDK in the areas studied, these differences are probably related to variation in occupation and exposure. Isolated reports of cases have also come from other parts of the world.^{13 17 36-40} However, many of these cases may have been spheroidal droplet degeneration rather than CDK itself.

The first report of this condition in Australia was made by McGuinness *et al.*⁴¹ They reported 51 cases seen in aboriginal males, all of whom had been stockmen for at least 20 years. Hollows⁴² found the prevalence to be 50% in the middle-aged men, but it was rare in females. Freedman¹³ also reported 2 cases from Australia. Taylor²⁰ reported a prevalence of 41% for aboriginal men over the age of 45 and 8% for aboriginal women aged 45 or more.

A number of reports documenting the pathology of climatic droplet keratopathy have now been published. The most comprehensive is that by Klintworth.⁴³ The most significant contribution to the understanding of the pathology of this puzzling condition has been made recently by Johnson and Overall,⁴⁴ who studied cases from Labrador with histochemical and antibody-labelling techniques. They demonstrated by immunoperoxidase studies that the droplets accumulate in the areas of the highest plasma-protein concentration. This, together with the fibrinoid tinctural properties and the strong evidence against a keratin or collagen derivation as shown by both Johnson and Overall and also by Klintworth,⁴³ suggests that the droplets are likely to be denatured plasma proteins.

In our study a number of interesting correlations were found between CDK and environmental factors. The association between occupation as a stockman for more than 20 years and climatic droplet keratopathy that McGuinness *et al.*⁴¹ posed was strongly confirmed in this study. However, the analysis failed to shed any direct light on possible causative factors. In one sense it has clouded the

issue by showing negative trends for some of the factors commonly regarded as potentially causative. This is probably because no account was taken of the variation in exposure to the different environmental factors that could occur in different groups. This study used the data available for the environmental parameters of each area and it did not measure the variation in exposure that does occur in those with different occupations.

No direct association was found between CDK and ultraviolet radiation or other factors likely to affect ultraviolet or other radiation levels such as latitude, hours of sunlight, or global radiation. In fact, there was a tendency for CDK to occur more often in areas with lower global radiation.

No association was found between CDK and factors indicative of dry or arid environments. In fact, the reverse trends were seen, although they were usually not statistically significant. CDK was found less commonly in arid areas with low rainfall, high evaporation rates, and low relative humidity. Although the role of microtrauma from dust or sand particles was not specifically examined, and data for wind strength and direction and dust-storm frequency were not available, the lack of association between the conditions that usually define areas likely to have dust storms, such as low rainfall, suggest that microtrauma is not likely to be a factor in causing CDK.

One explanation for the relatively lower prevalence of climatic droplet keratopathy in the more inhospitable climates may have been that these areas were also unsuitable for cattle raising, and therefore there would not be stockmen working in these areas. It was for this reason that the subgroup of those stockmen who had worked for more than 20 years was examined. Although the numbers were not large in this group, no direct evidence emerged that would indicate a causative factor for CDK. Except for occupation, the study was unable to substantiate the importance of any of the factors previously thought to be associated with the development of climatic droplet keratopathy.

By observation of stockmen at work the potential causative factors that seem relevant are exposure to sunlight (including ultraviolet light) and to dust. Aboriginal stockmen differ from the European stockmen in that the Europeans do not usually spend more than a few years continuously working with cattle in the outback. After a few years a European usually will either move elsewhere or become a station manager, and therefore will not spend as many years continuously moving and mustering cattle. Aboriginal stockmen differ from other Aborigines in that they usually work through the heat of the day, often in shadowless plains,

and are therefore not able to rest under the shade of a tree, wiltja, or shed as other Aborigines are able to do whether they are employed or not. Exposure to dust occurs particularly at the time of yarding. While it is true that aboriginal children are often around the cattle mustering yards, they do not spend long hours there, and women are rarely seen there. Again, these tasks are performed mainly by the aboriginal stockmen, only sometimes being overseen by a European manager.

Although it is one thing to measure the environmental factors as they affect an area, it is another thing to measure the actual exposure that various individuals receive. No data are available for the amount of ultraviolet radiation received by those working as stockmen, as compared to other people living in the same area. It would appear that the environmental ultraviolet radiation is sufficient to cause climatic droplet keratopathy anywhere in the areas studied if a person receives sufficient outdoor exposure. It would appear that (as a group) stockmen who work continuously through the hottest part of the day and therefore receive the longest ultraviolet exposure are the only ones who receive sufficient radiation to induce the changes recognised clinically as CDK.

A possible mechanism of action of ultraviolet radiation has been proposed by Johnson and Overall.⁴⁴ They have suggested that plasma proteins, especially albumin, IgG, and IgA, are affected or denatured by ultraviolet radiation as they diffuse through the cornea. This results in their deposition and accumulation. Because these proteins are most concentrated in the corneal periphery, it is not surprising that their accumulation should be first seen in that area. The distribution in the palpebral fissure is entirely consistent with a direct radiation effect, as is the initial superficial location.

The amount of radiation a person receives is likely to be even more relevant if the ocular changes in CDK noted by Johnson and Overall⁴⁴ do in fact represent altered plasma proteins. It would then follow that the longer the exposure to ultraviolet radiation, the more altered protein would accumulate, leading eventually to those changes recognised clinically as CDK. Further, the more continuous the exposure, the less time there is available for reabsorption of altered proteins or the possibility of a 'dark repair' process to clear the deposits during times of reduced exposure or at night.

One must conclude that, although it is not possible to identify with certainty the causative factor in climatic droplet keratopathy, it is almost surely a result of environmental exposure. There is strong circumstantial evidence that ultraviolet radiation is the causative factor.

The relation between latitude and pterygium proposed by Cameron²⁷ was confirmed. The correlation seen with ultraviolet B radiation had been postulated before but had not been previously demonstrated. Anderson²¹ postulated a causal relation between temperature and pterygium, and this study also showed a weak association between annual maximum temperature and pterygium. A trend for pterygium to be associated with higher evaporation rates was also found, although a clear relation did not exist between pterygium and humidity. The association between hours of sunlight and the global radiation in general may well represent a secondary association of these factors to latitude and ultraviolet radiation.

Following examinations conducted in Finland, Lapland, Iceland, Greenland, Northern Canada, Alaska, and Cheremis (USSR) Forsius suggested that, for pterygium to develop, a low humidity and the presence of microparticles were required as well as sufficient ultraviolet light, whereas CDK would develop in areas of high humidity and without many microparticles.¹⁸

Garner *et al.*¹⁰ however, came to an opposing conclusion in that they considered that climatic extremes and trauma from dust or ice particles resulted in CDK and that sun exposure without microtrauma by dust caused other lesions, particularly pinguecula and, by inference, pterygium.

Wong⁴⁵ has suggested the possibility of a pterygium angiogenesis factor which develops following repeated irritation along the corneal-limbal junction. The presence of this factor leads to the formation of pterygium. While he examined the role of such a factor, he did not inquire into its origin. It may well be that prolonged ultraviolet exposure causes histological changes in the proteins of Bowman's membrane²⁷ and that these altered proteins can then act as the stimulating factor.

The present study would indicate that the development of pterygium is indeed related to ultraviolet exposure and that pterygia are more likely to develop in a hot dry environment. Further, while it is not possible clearly to identify the aetiological factors for CDK, clear evidence of the environmental nature of this condition is shown, and circumstantial evidence would implicate ultraviolet radiation.

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Corneal endothelial changes under induced intraocular pressure elevation: a scanning and transmission electron microscopic study in rabbits

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SUMMARY Intraocular pressure was artificially raised to 60–70 mmHg in 7 albino rabbits for periods of 15 minutes to 4 hours. The corneal endothelium of these eyes was studied by transmission and scanning electron microscopy. A correlation between exposure time to elevated IOP, clinical signs observed by slit-lamp examination, and extent of morphological damage is clearly shown. In eyes exposed to high pressure for 15 and 30 minutes corneas remained transparent and only minimal changes could be detected by SEM, which consisted of small areas of cells with unevenness of their surface, occasional cellular ruptures, and diminution of cilia and microvilli. After 1–2 hours of exposure small, solitary corneal opacifications appeared. In these eyes more severe morphological changes affecting larger areas were observed, with additional cellular blebbing, excariocytosis, cellular rupture, disintegration, and disappearance seen in SEM. Thin sections revealed swelling of mitochondria, disorganisation of endoplasmic reticulum, and the existence of myelin bodies. In eyes exposed for 3 and 4 hours to high IOP diffuse corneal haziness, implying stromal oedema, appeared. In these eyes the areas affected were larger, the extent of damage being more severe. Many areas were bare of endothelium, surrounded by scattered cellular debris, and showed cells with ballooning surfaces and multiple ruptures. Even in severe cellular damage cellular junctions appeared intact. It is assumed that endothelial cells are more sensitive to IOP elevation than the cellular junctions and that injury to the active pump system due to morphological damage is responsible for the resultant corneal oedema.

It is widely accepted that endothelial integrity and metabolic activity are essential for continuous maintenance of corneal dehydration and transparency. On the one hand the endothelium is the site of a metabolically dependent fluid pump that counteracts fluid leakage, while on the other it acts as a barrier to solutes from the anterior chamber.^{1–5} Corneal oedema accompanying acute glaucoma was shown to result from noncompensated corneal endothelium.^{1,2,4–6} This noncompensation, which allows excessive flow of fluid to the corneal stroma, might be explained by two mechanisms: (1) High intraocular pressure (IOP) affects the metabolic active-pumping mechanism without any morphological changes, thus reducing resistance to aqueous flow to the stroma with resultant stromal oedema.⁵ (2) Elevated IOP causes morphological cellular

damage, thus reducing anatomically and functionally the barrier to flow of fluid into the stroma. In 47 eyes with chronic glaucoma decreased concentration of endothelial cells along with progressive atrophy and degeneration were described.⁶

More recently other investigators using scanning electron microscopy (SEM) and transmission electron microscopy (TEM)^{7–10} have shown various morphological changes which could be attributed to the nonfunctioning endothelium. Among these changes were flattening of cells, blebbing of cellular surface, intracellular vacuolisations, nuclear expulsion (excaryocytosis), and complete endothelial disorganisation or disappearance.

All these morphological changes were clearly shown by Svedbergh¹⁰ in monkey eyes exposed to moderate IOP (33–44 mmHg) for 3–7 hours. However, in that study the IOP was elevated by adjusting the height of a reservoir containing mock

aqueous humor connected to the anterior chamber. Although it is acceptable that high IOP was the main cause for the morphological changes described, some additional damage could be attributed to the perfusion of the anterior chamber. Perfusion of the cornea *in vitro* with Ringer bicarbonate without application of high pressure resulted in variable ultrastructural changes such as vacuolisation, mitochondrial and endoplasmic reticulum swelling, and complete intracellular disorganisation.¹¹

The purpose of the present study was to investigate the extent and character of endothelial ultrastructural changes in relation to different exposure periods of elevated IOP and the extent of the resulting stromal oedema. In order to minimise possible damage due to perfusion and turbulence near the endothelium the IOP was artificially elevated by connecting a reservoir of normal saline to the vitreous through the pars plana.

Materials and methods

Seven albino rabbits of 2.5–3.5 kg body weight were anaesthetised by injection of pentobarbitone sodium (30 mg/kg) intravenously. After deep anaesthesia was achieved the IOP was artificially elevated in the right eye, the left eye serving as a control. IOP elevation was carried out by connecting a reservoir of normal saline through the pars plana to the vitreous. The height of the reservoir was adjusted between 81 and 95 cm, creating an IOP of 60–70 mmHg. The rate of IOP elevation was verified by measurement with hand-held applanation tonometer (Perkins).

To eliminate the possible effect of saline perfusion 2 control eyes were connected to the reservoir adjusted to a height of 10 cm, keeping IOP within normal limits. During the period of IOP elevation we carried out slit-lamp examination, looking for signs of corneal oedema, ciliary congestion, flattening of the anterior chamber, pupillary diameter, and its reaction to light. Eyes examined were exposed to different period of IOP elevation, lasting 15 minutes, 30 minutes, 1 hour, 90 minutes, and 2, 3, and 4 hours.

At the end of the exposure time both eyes were enucleated and buttons of cornea were immediately cut from the globe. The corneas were immersed in 2% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, and fixed at 4°C overnight. For thin sectioning and TEM the tissue was postfixed in 2% OsO₄ in the same buffer and embedded in Epon. Thin sections on grids were stained with uranyl acetate and lead citrate. Preparations were examined and photographed in a Jeol-100B electron microscope at 80 kV. For SEM fixed pieces of cornea were

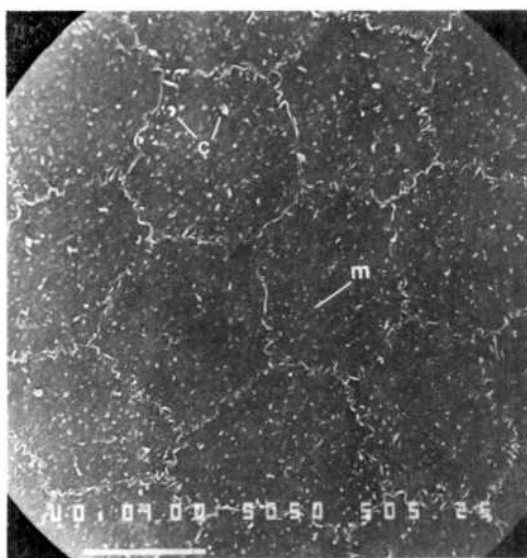


Fig. 1 Normal corneal endothelium (SEM). Cells are flat, hexagonal in shape, with randomly distributed microvilli (M) and cilia (C). Note the sharply demarcated intercellular borders. $\times 3000$.

postfixed with OsO₄ as above, washed and dehydrated in a series of ethyl alcohols. Drying was carried out from liquid CO₂ by the critical point method. After drying, preparations were coated with either gold or gold-palladium (60–40%) by sputtering and photographed in a Jeol-S35 scanning electron microscope at 20–25 kV.

Results

On slit-lamp examination slight corneal opacification could be detected after 1–2 hours of exposure to high IOP. Diffuse stromal oedema appeared only after 3–4 hours of exposure. Ciliary congestion could be observed after 30 minutes, while pupillary mid-dilatation and nonreaction to light could be detected only after 1 hour. Flattening of the anterior chamber was noticed immediately.

In the control eyes (including the 2 eyes perfused with saline) the endothelial appearance resembled previously reported descriptions.^{12–15} In TEM the cells appeared flat, with numerous mitochondria and organised rough endoplasmic reticulum. Apical tight junctions were observed between cells with occasional pinocytotic vesicles and cilia on the cell surface. In SEM endothelial cells appeared flat, hexagonal in shape, with randomly distributed microvilli and cilia on the cell surface. Sharply demarcated, interdigitating cellular borders were also observed (Fig. 1). In eyes exposed for 15 and

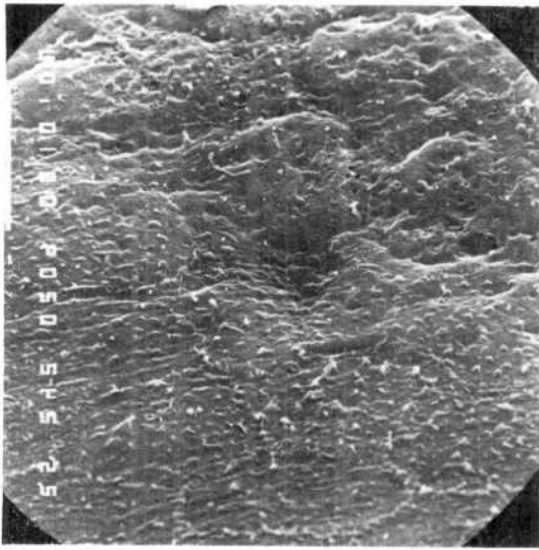


Fig. 2 Border area between nonaffected endothelium (bottom) and minimally damaged cells after 15 minutes of exposure to elevated IOP. Note unevenness of cellular surface and diminution of microvilli and cilia. $\times 3000$.

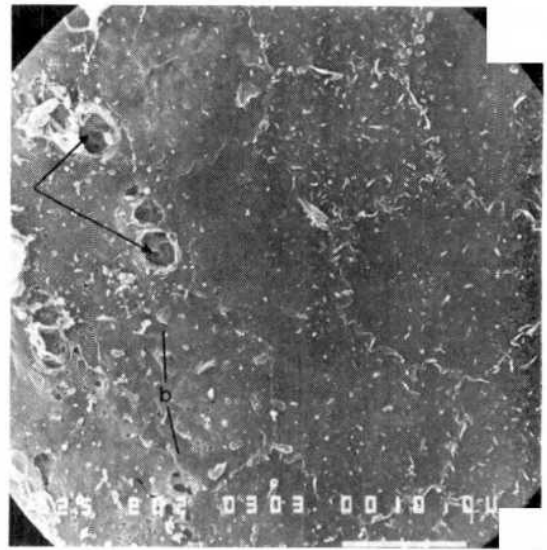


Fig. 3 Minimal damage to endothelium after 30 minutes of elevated IOP. Normally appeared endothelium (right) is adjacent to cells with attenuated cell surface, blebbing (b), and cellular ruptures (arrows). $\times 3000$.

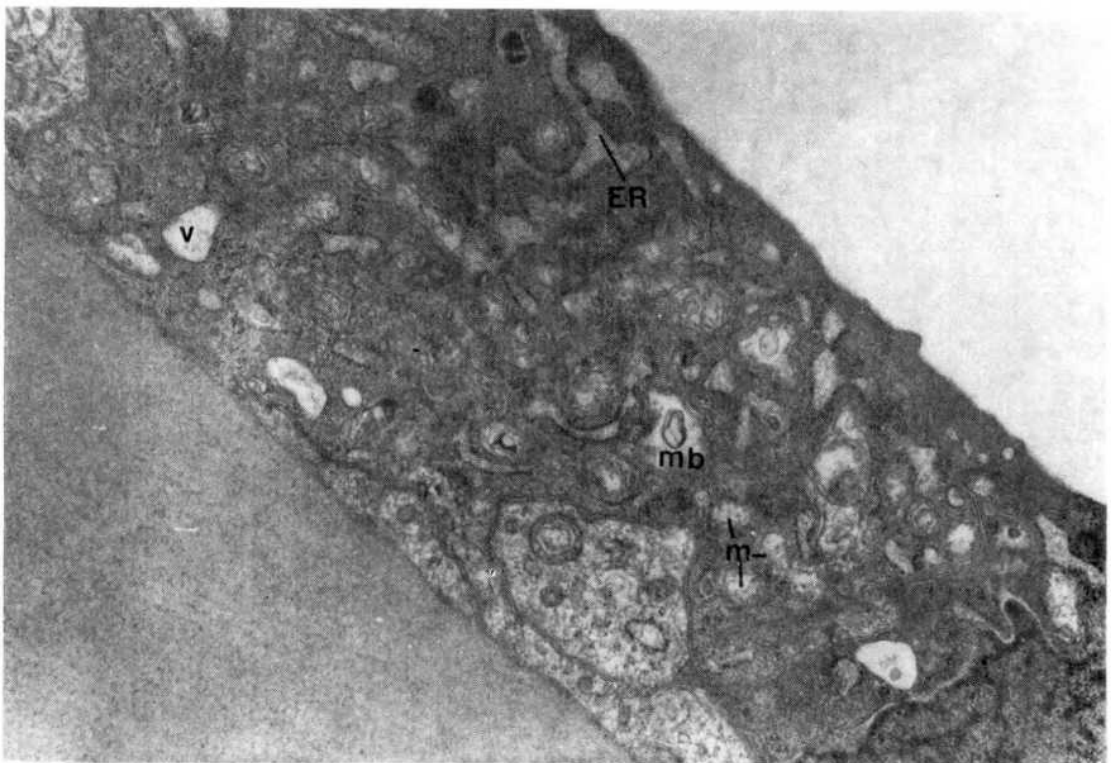


Fig. 4 Endothelial cell after exposure of 1 hour to high pressure. Distention and swelling of mitochondria (M) and endoplasmic reticulum (ER) is evident. Note vacuolisations (V) and myelin body (MB). $\times 18\,000$.

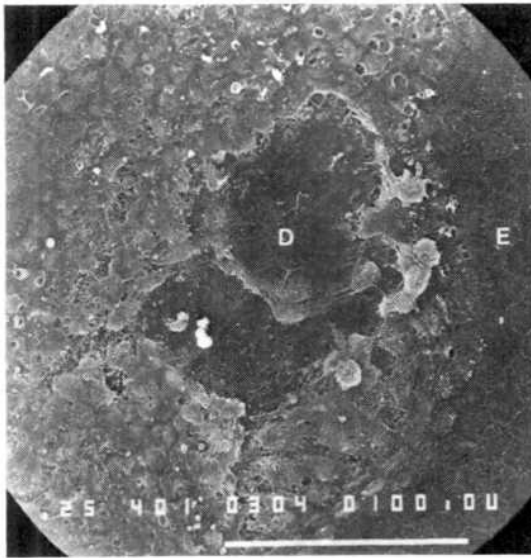


Fig. 5 An area of severely damaged endothelium after exposure of 4 hours to elevated IOP. The centre of insulated area is devoid of endothelium (D), surrounded by ruptured cells and cellular debris. At right normal endothelium (E) is seen and at left minimally damaged cells are shown. $\times 750$.

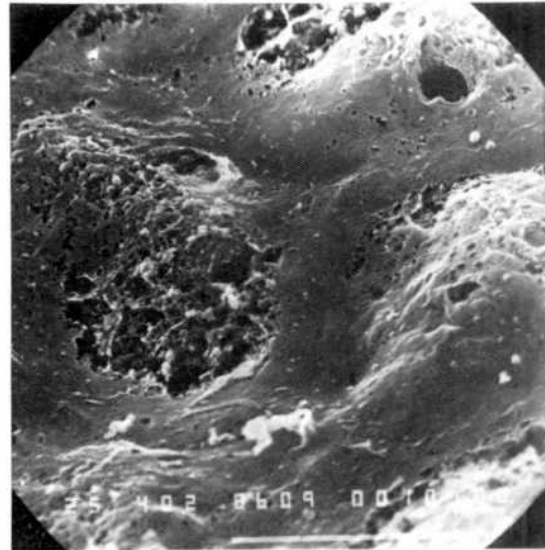


Fig. 6 Severely damaged endothelium. Ruptured cell containing empty crater after nuclear expulsion. $\times 6000$.

30 minutes to elevated IOP only anterior chamber flattening and ciliary congestion were observed by slit-lamp examination. No signs of corneal oedema or regional opacification were detected. Thin sections of the endothelial cells in these eyes were completely normal. In SEM only minimal changes could be seen. Most of the cells appeared normal, but in small, scattered areas unevenness of cellular surface along with slight swelling of cellular content were evident. Occasional ruptured cell surfaces were encountered. Cilia and microvilli were observed less frequently (Figs. 2, 3).

In eyes exposed for 1–2 hours to high pressure, small solitary corneal opacifications could be seen on slit-lamp examination, along with pupillary mid-dilatation and nonreaction to light. Increased ciliary congestion and anterior chamber flattening were also observed. Eyes exposed to high IOP for 3 and 4 hours showed further deterioration of corneal opacification to more diffuse haziness, indicating progression of corneal oedema.

In thin sections affected cells showed disorganisation and swelling of endoplasmic reticulum and mitochondria along with vacuolisations and myelin bodies (probably evidence of cellular destruction) (Fig. 4). Despite intracellular damage junctional complexes appeared intact, unaffected by acutely elevated IOP.

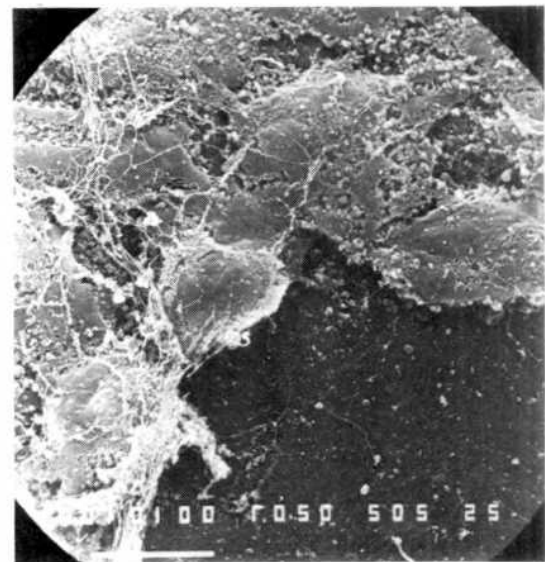


Fig. 7 Severely damaged endothelium. Bare area (Descemet's membrane) surrounded by ruptured disintegrated cells. $\times 3000$.

SEM, enabling the observation of large areas of the affected endothelium, disclosed different types of cellular damage. It was evident that larger areas of the endothelium were damaged when the eyes were exposed to elevated IOP for 3–4 h. Moreover, it was possible to monitor different types of mor-

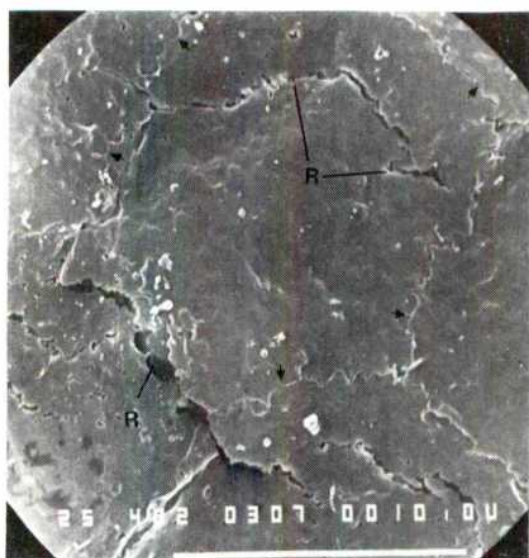


Fig. 8 Rupture of cellular surfaces. Rupture planes (R) leave intercellular junctions (arrow-heads) intact. $\times 7250$.

phological changes in correlation with the exposure time to high pressure.

Along with the slight morphological changes (unevenness of cellular surface and diminution of cilia and microvilli) more severe changes appeared. These included blebbing and ballooning of cell surface, cellular swelling, nuclear expulsion (excaryocytosis), ruptured cells containing empty craters and scattered cellular content, disorganised cells and completely bare areas of Descemet's membrane devoid of endothelium, which had completely disappeared (Figs. 5–7). In some areas rupture of cellular surfaces could be noticed without blebbing or nuclear expulsion. It was evident in these cells that rupture planes passed through cellular surface only, leaving the intercellular borders intact (Fig. 8).

Discussion

In our study a good correlation between exposure time to elevated IOP, clinical signs, and extent of morphological changes was noted. After minimal exposure time (15 and 30 minutes) the cornea remained transparent, and only minimal morphological changes were detected in SEM (attenuation of cell surface, loss of cilia and microvilli, and occasional ruptures in small areas). After 1–2 hours small opacities appeared and more extensive damage was observed. In these eyes small areas of nuclear expulsion, cell rupture, and endothelial disintegration were encountered. In thin sections mitochondrial and endoplasmic reticulum swelling

and disorganisation were evident, indicating damage to essential metabolic processes. In eyes exposed for 3 and 4 hours additional cellular disintegration, rupture and disappearance could be seen, along with progression of corneal opacification leading to diffuse oedema. It seems that cellular integration is essential to the proper action of the pump mechanism. The fact that despite severe cellular damage the tight junctions appeared intact stands out. It reconfirms previous postulations that these junctions are not the main contributors to the barrier against leakage of fluid.^{4,16}

In the normal eyes the corneal endothelium acts as a barrier to fluid leakage into the stroma from the anterior chamber. This is carried out mainly by an active pumping system, which counteracts the passive leakage to the stroma.^{1–5,17} Ouabain, an inhibitor of Na^+/K^+ activated ATPase system, had been demonstrated to cause corneal swelling when applied to the endothelium.¹⁸ Further, an adequate ATP level was found to be required for transport activity.⁴ Thus it is believed that the active pump mechanism is Na^+/K^+ ATPase dependent. In addition the existence of apical tight junctions between endothelial cells is believed to contribute to the 'sealing off' effect, though several investigators claim that a passive leakage through these junctions is possible and that this leakage is counteracted by the active pumping system.^{4,16} Perfusion of the cornea with Ca^{++} -free medium caused corneal swelling and TEM disclosed disintegration of junctional complexes.^{19,20} It was also found that large molecules (such as the colloidal tracer ThO_2) can bypass the junctional complexes via pinocytotic vesicles.²¹

It is likely, however, that in addition to the main mechanism of active pumping the junctional complexes serve as passive barriers to fluid leakage, and pinocytosis helps in transferring large molecules across the endothelium, if necessary. Leber²² was the first to describe localised endothelial defects corresponding to spots of corneal opacity in a rabbit under IOP of 110 mmHg. Kaye *et al.*, studying corneal behaviour in vitro under pressure of 60–80 mmHg, found the endothelial barrier to deteriorate before the metabolically dependent pump mechanism fails. TEM revealed no morphological changes (duration of high pressure was not stated).⁵ More recent morphological studies using TEM and SEM disclosed flattening of cells, blebbing of cellular surface, excaryocytosis, and endothelial disintegration.^{7–10}

It seems that for a diffuse corneal oedema to develop a certain threshold of decompensation must be reached. We believe that unaffected endothelium in eyes exposed to high pressure for short

periods can compensate for the rather small damaged and leaky areas, thus keeping corneal stroma dehydrated and transparent. However, if the extent of damage is more severe, as seen in eyes exposed for longer periods, the remaining functioning endothelium loses its ability to compensate for the larger leaking areas, and a diffuse corneal oedema results. In the rabbit cornea under IOP of 60–70 mmHg this decompensation appears after 3 to 4 hours of exposure.

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Bilateral necrotising scleritis with marginal corneal ulceration after cataract surgery in a patient with vasculitis

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SUMMARY The onset of bilateral necrotising scleritis and marginal corneal ulceration after cataract surgery are described in a patient with diffuse vasculitis syndrome. The finding of immune complexes in this patient's tissue biopsy suggests that they are the cause of a localised primary vasculitis triggered by surgical inflammation. Clinically, this patient's marginal corneal ulceration preceded the scleral necrosis. A past history of orbital inflammation may have been due to a posterior scleritis. The corneal ulcerations responded to conjunctival debridement and steroids. The scleral necrosis was unresponsive to the 2 anti-inflammatory preparations tried, and the patient eventually went into remission while off all treatment.

Necrotising scleritis is the most serious and destructive form of scleral disease. It is rare and often associated with a variety of systemic disorders. This case report documents the onset of bilateral necrotising scleritis and marginal corneal ulceration after cataract surgery in a patient with a diffuse vasculitis syndrome. Immune complexes found in the conjunctiva and episcleral tissue may have been instrumental in triggering the inflammatory process.

Case report

A 67-year-old white female with a vasculitis syndrome presented for ophthalmological evaluation of painless, progressive loss of vision in both eyes. Her systemic disease began 3 years earlier with fever, chest pain, anaemia, and evidence of renal failure. A renal biopsy showed 'focal lobular glomerulitis'. Early in the course of her illness chronic serous otitis of the right ear required treatment with a Teflon tube tympanectomy. Methylprednisone therapy was instituted and maintained continuously. The association of a vasculitis syndrome after acute otitis media has been reported.¹ At the time of ophthalmological consultation

(March 1977) the dose of methylprednisone was 48 mg and 32 mg on alternate days.

Two years before this eye examination she had what was diagnosed as a left orbital inflammation, which resolved without sequelae on systemic corticosteroids. That episode started with a limitation of elevation of the globe and was accompanied by lid oedema and chemosis. An ultrasonogram at that time revealed thickening of the extraocular muscles.

Her general physical examination when first seen at the New York Hospital-Cornell Medical Center showed a thin, frail-appearing woman confined to a wheelchair because of severe weakness and pain due to fractures of the left pubic ramus. Her blood pressure was 160/90 mmHg, there were ecchymotic skin lesions over the extremities, and she had a mild left hemiparesis. Notable laboratory data were: haematocrit 23; serum creatinine 2.2 mg/100 ml (194 µmol/l) a trace of protein in the urine; latex fixation test negative; hepatitis B surface antigen negative.

Ocular examination showed a best corrected visual acuity of counting fingers at 5 ft (1.5 m) on the right and hand motions on the left. Schirmer testing showed an adequate tear volume in both eyes, though slit-lamp examination revealed some filament formation on the left cornea, suggestive

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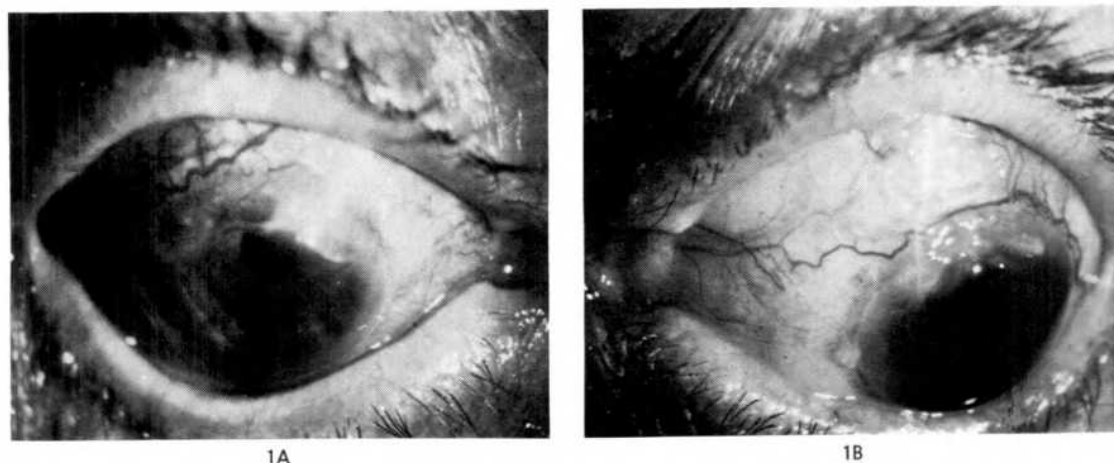


Fig. 1A Marginal corneal ulceration and infiltration of the right eye. B: Similar corneal ulceration and early scleral necrosis of the left eye. There is prominent vessel formation in the limbal area.

of a tear volume deficit. There was no corneal infiltration or inflammation of the anterior chamber. There were dense lens opacities in both eyes, the left greater than the right. There was no sign of present or past scleral inflammation. The intraocular pressure was 17 mmHg in each eye. Indirect ophthalmoscopy through the dense lens opacities revealed a normal disc, vessels, and macular area in each eye.

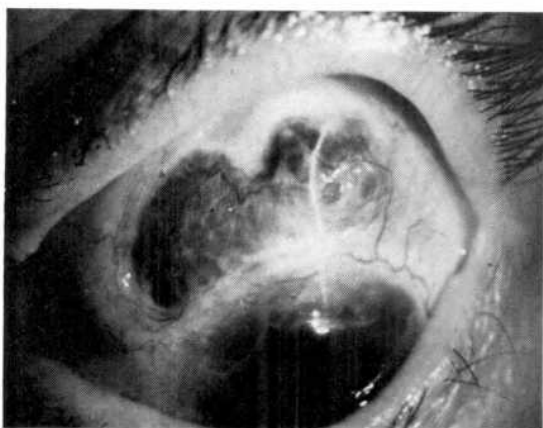
The patient underwent an uncomplicated left intracapsular lens extraction on 18 May 1977. The wound was closed with 5 buried 8-0 silk sutures beneath a limbal flap. She had an uncomplicated postoperative course and was maintained on atropine 1% drops 4 times a day, chloramphenicol drops 4 times a day, and dexamethasone phosphate drops twice a day for 5 weeks. The second or right eye underwent a similar uncomplicated cataract extraction 6 weeks after the first operation. The same technique with silk sutures was used. Three months after her last operation she was comfortable and seeing 20/25 in both eyes from her aphakic spectacles. The eyes were uninflamed except for some injection at each limbal area.

She returned 3 weeks later complaining of discomfort in both eyes. Examination of the right eye revealed erosion of a suture at the 11 o'clock position 1 mm from the limbus. There was also some peripheral corneal infiltrate from the 11-1 o'clock position. Examination of the left eye showed only erosion of a suture through the conjunctiva at the 10 o'clock position of the limbus. The superior limbal conjunctiva of each eye appeared somewhat oedematous. We thought we might be dealing with a peripheral staphylococcus corneal infection and/or

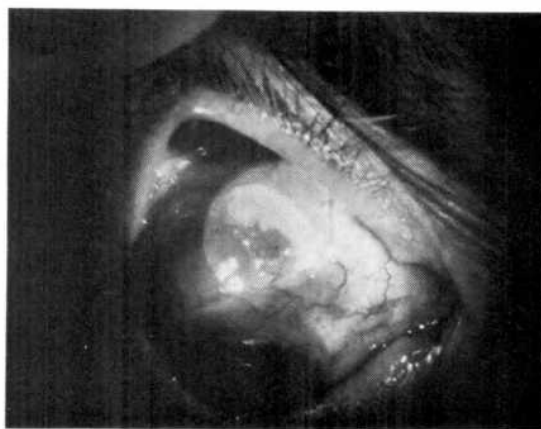
a suture abscess. The exposed sutures were removed and topical chloramphenicol treatment was instituted. Culture of each eye showed only a few colonies of *Staphylococcus epidermidis*.

One week later the patient returned with more corneal infiltrate on the right and the start of infiltrate on the left. Reculture showed no organisms. She was started on topical dexamethasone every 2 hours. A week later she returned still very uncomfortable, with the process of peripheral corneal infiltration continuing. The limbal conjunctiva looked more inflamed and oedematous. The remaining buried sutures were removed in the office at the slit-lamp, and the patient continued on topical corticosteroids every 2 hours while awake and chloramphenicol eye drops 4 times a day. The remaining sutures were removed because it was thought they might be playing a role in the continuation of this uncontrolled inflammation. She returned 5 days later with more peripheral corneal infiltrate, loss of corneal stroma in each eye, and scleral melting on the left, radiating from the original 10 o'clock suture tract (Figs. 1A and B).

At this time we decided to debride the oedematous, inflamed, and necrotic-appearing limbal conjunctiva for therapeutic and diagnostic purposes. The patient was admitted to the New York Hospital and taken to the operating room. The friable conjunctiva and episcleral tissue over each limba area were surgically resected in the form of an ellipse concentric to the limbus. The superior 180° from the limbus to 4 mm posterior was removed in each eye. The tissue was placed in appropriate media and sent for histological and immuno-



2A



2B

Fig. 2A Advanced scleral necrosis with healing of the marginal corneal ulcerations in the left eye. A characteristically white avascular rim of necrosis is present. B: Fluorescein stain shows residual area of scleral necrosis in the right eye.

fluorescent studies. Postoperatively the patient was placed on hourly topical dexamethasone in each eye around the clock for 1 week, which was gradually tapered off as the corneal infiltrate disappeared. Three weeks after removal of the conjunctiva the corneas cleared of infiltrate, developed epithelium, and the patient became much more comfortable. The scleral melting continued in the left eye insidiously (Fig. 2A).

It was difficult to convince the patient that she still had a serious problem, since she was now comfortable and the eyes were less injected. She was started on oral indomethacin, 100 mg per day in divided doses, to control the scleral necrosis. The topical corticosteroids were continued once a day in each eye. The scleral necrosis continued. After 1 month the patient was started on oxyphenbutazone, 600 mg per day in divided doses. The scleral necrosis continued on the left and became worse on the right. This medication was discontinued when no effect was shown after 3 weeks. No other medication was given at this time because of a drop in the patient's platelet count. The scleral necrosis continued for 1 month while the patient was off all medication and then suddenly stopped in the left eye and slowed in the right (Fig. 2B). She has now been stable for the last 6 months.

HISTOPATHOLOGICAL FINDINGS

Microscopically the arteries, arterioles, and veins in the conjunctival-episcleral biopsy were surrounded by a cellular infiltrate consisting of polymorphonuclear neutrophils, lymphocytes, eosinophils, and in some areas plasma cells. The walls of some vessels were extensively infiltrated by

inflammatory cells (Figs. 3A and B). In addition, margination and diapedesis of polymorphonuclear neutrophils were present.

Frozen sections of the biopsy which had been embedded in gelatin were treated with fluoresceinated rabbit antisera to human IgG, IgA, IgM, IgE, C3, and fibrinogen. Examination of these sections revealed focal granular deposits of IgG (Fig. 3C) IgM, and C3 (Fig. 3D) in the walls of conjunctival vessels, indicating that immune complexes had been deposited. In addition fibrin was deposited focally in vessel walls, presumably at sites of injury (Fig. 3E).

Discussion

Necrotising anterior scleritis is a rare and destructive disease resulting in necrosis and disappearance of the scleral envelope of the eye.² Its occurrence after cataract extraction is unusual. The finding of immune complexes in the inflamed tissue suggests that they are the cause of localised vasculitis in this patient.

In the biopsied conjunctival tissue of this patient polymorphonuclear neutrophils and eosinophils were adherent to the endothelium of many vessels and were seen between endothelial cells, presumably attempting to phagocytose immune complexes deposited in the lining and in the walls of these vessels. It has been shown that, when polymorphonuclear leucocytes attempt to ingest immune complexes on nonphagocytosable surfaces such as vascular membranes, lysosomal enzymes are released into the surrounding tissues.^{3,4}

The question arises as to why immune complexes

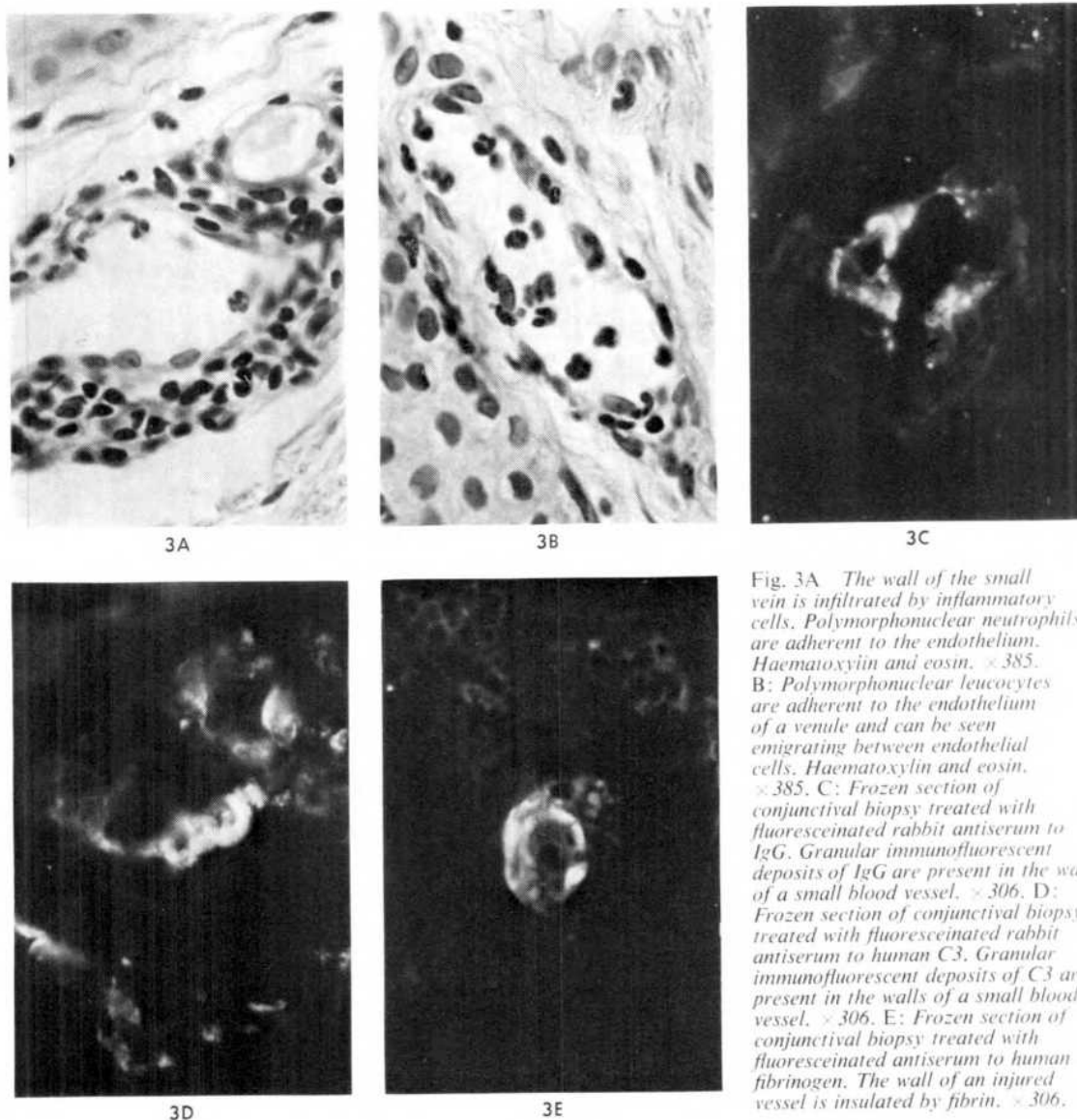


Fig. 3A The wall of the small vein is infiltrated by inflammatory cells. Polymorphonuclear neutrophils are adherent to the endothelium. Haematoxylin and eosin. $\times 385$. B: Polymorphonuclear leucocytes are adherent to the endothelium of a venule and can be seen emigrating between endothelial cells. Haematoxylin and eosin. $\times 385$. C: Frozen section of conjunctival biopsy treated with fluoresceinated rabbit antiserum to IgG. Granular immunofluorescent deposits of IgG are present in the wall of a small blood vessel. $\times 306$. D: Frozen section of conjunctival biopsy treated with fluoresceinated rabbit antiserum to human C3. Granular immunofluorescent deposits of C3 are present in the walls of a small blood vessel. $\times 306$. E: Frozen section of conjunctival biopsy treated with fluoresceinated antiserum to human fibrinogen. The wall of an injured vessel is insulated by fibrin. $\times 306$.

were deposited in conjunctival-episcleral vessels in this patient, who at this time had no clinical evidence of immune complex deposition in other vascular beds, such as renal glomeruli. We have no answer to this, but we can offer 2 hypotheses.

The first hypothesis concerns the nature of the blood vessels of the external eye in this patient. Corneal and scleral necrosis began after the patient underwent surgery for cataracts. New vessels proliferated during healing of the wound occurred, and it is in this new area that immune complexes were deposited (Fig. 2B). This may indicate that

new vessels are more susceptible to deposition of circulating immune complexes. If this is true, it would explain the progressive nature of the disease, since a situation would be created in which injury would follow reparative vessel growth as long as immune complexes remained in the circulation. According to this hypothesis patients with circulating immune complexes would be at particular risk of developing the scleral necrosis syndrome, not because of defective healing but because of increased vulnerability of new vessels.

The second hypothesis, which is not exclusive

of the first, concerns the nature of the patient's circulating immune complexes. Although we could not demonstrate cryoglobulinaemia during the period of her illness described above, cryoglobulinaemia had been demonstrated in the past during periods of clinically active systemic disease. Cryoglobulin complexes might be expected to be deposited selectively in superficial vessels of the external eye, where the temperature would be lower than in vessels of internal organs. The two hypotheses together suggest the progression of scleral necrosis in this patient may have been a result of synergy between the increased susceptibility of new blood vessels to immune complex deposition and the thermal optimum for precipitation of cryoglobulins.

This hypothesis also suggests that patients with a history of rheumatoid arthritis, lupus erythematosus, or other diseases associated with circulating immune complexes might be at a special risk of developing scleral melting after ophthalmic surgery and should be examined for the presence of circulating complexes by a variety of techniques now available.

Our patient presented initially with discomfort and signs of marginal corneal ulceration. With resolution of the corneal involvement the symptoms subsided, but the destructive scleral process continued in an insidious manner, revealing the correct diagnosis of necrotising scleritis.

The corneal changes are similar to a Mooren's ulcer, which one might consider in the diagnosis in the absence of scleral involvement. Both types of ulcers are painful and gradually progressive. Mooren's ulceration, however, is not associated with any systemic disease or progressive scleral ulceration.⁵

The patient's past episode of left orbital cellulitis, presenting first with a limitation of elevation, may have been due to an unrecognised posterior scleritis. Inflammation of the posterior sclera is a difficult diagnosis to make and is deduced from its secondary effects on neighbouring tissues. The patient

presents with pain, limitation of ocular movements, chemosis, and sometimes lid oedema. The indirect consequence of inflammation provides the clue to diagnosis, but its appearance will often simulate orbital cellulitis or pseudotumour formation. Bertelsen⁶ confesses to this mistake in diagnosis in 6 out of 12 patients.

The treatment of deep scleritis at various stages is controversial. Watson and Hayreh² believe that scleritis is medically treatable provided the dosages of the drugs are adequate to suppress the inflammatory change. Aronson and Elliot disagree.⁷

Many anti-inflammatory agents are now available, but only a few are effective in the treatment of scleral disease. These include corticosteroids, indomethacin, and oxyphenbutazone. Some difficult cases have responded to cytotoxic agents.⁸ Our patient did not respond to indomethacin or oxyphenbutazone. She underwent a spontaneous remission after being off systemic medications for 1 month. The controversy surrounding the treatment of deep scleritis is probably due to its unpredictable course.

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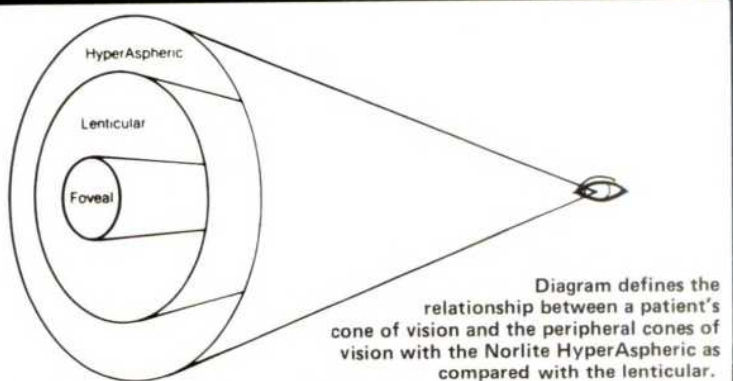
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Brittle cornea, blue sclera, and red hair syndrome (the brittle cornea syndrome)

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SUMMARY A syndrome of red hair, blue sclera, and brittle cornea with recurrent spontaneous perforations is presented in 2 siblings of a Tunisian Jewish family. The genetic transmission of this disorder is autosomal recessive. This is the second description of this syndrome, which should be called the 'brittle cornea syndrome'. This syndrome has so far been reported only in Tunisian Jewish families.

Brittle cornea with spontaneous perforation is a rare disease. It has been described in association with systemic mesodermal disorders such as osteogenesis imperfecta,¹ Marfan syndrome,² and Ehlers-Danlos syndrome.³

This communication describes a 'brittle cornea' syndrome unrelated to systemic mesodermal disorders. The triad of symptoms includes red hair, brittle megalocornea, and blue sclera. The following 2 cases and the 4 other cases reported previously⁴ represent the above syndrome without any systemic manifestations.

The 'brittle cornea' syndrome seems to be an isolated genetic disorder transmitted as an autosomal recessive trait.

Case reports

Two children out of 5 siblings presented the following disease. The parents were first cousins and originated from a Tunisian Jewish family. Both patients had red hair (Figs. 1, 5), blue sclera, and uniform keratoglobus, and extremely thin corneae (Fig. 3) with several leucomata from previous spontaneous perforations (Figs. 4, 7, 8). On physical examination both children appeared otherwise normal. No systemic manifestations were found, and blood examinations gave normal results. The parents and other members of the family had dark hair and no abnormality of the eyes.

Patient 1 was a red-haired boy, 16 years old (Figs. 1, 2). In the past he had a spontaneous perforation of his left cornea, which had been repaired surgically. On examination the right eye had a

visual acuity of 6/60 with the best myopic correction. The cornea was extremely thin with keratoglobus (Fig. 3). The anterior chamber was deep and the lens was clear. No abnormalities were present in the posterior segment. The intraocular pressure was 16 mmHg.

Examination of the left eye revealed a visual acuity of counting fingers at 2 meters. A large corneal scar was present in the centre of the left cornea with anterior iris adhesions (Fig. 4). The lens remained clear. Fundus examination, so far as could be seen, did not reveal any abnormality.

Patient 2 was a red-haired girl, 8 years old (Figs. 5, 6). She had had recurrent perforations of her eyes, which were surgically repaired. The visual acuity was found to be counting fingers at 1-2 meters due to a central corneal adherent leucoma in each eye (Figs. 7, 8). The lenses and posterior segments were normal so far as could be seen.

Family studies. The parents of the children were first cousins. Both were healthy, without any ocular abnormality. Of their 5 children 3 were normal and two affected. All members of the family except the 2 affected children had dark hair and none had blue sclera, bone fractures, or deafness. The examination of the family could not be extensive because most members live in Tunis. However, only the 2 children described above were red-haired and affected by eye disease. Fig. 9 illustrates the family tree.

Discussion

This brother and sister and 4 other cases previously reported⁴ present a triad of symptoms of red hair, blue sclera, and brittle cornea. Systemic mesodermal

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drome, for example, deficiency of lysyl hydroxylase activity in cultured fibroblasts has been reported.³⁻⁹ However the deficiency of this enzyme in similar cases has not been confirmed by others.¹⁰⁻¹¹ Unfortunately such biochemical assays were not performed in our cases. However, they did not present bone fractures or deafness as in osteogenesis imperfecta. Nor did they present skin or ligament hyperelastic changes as in Ehlers-Danlos syndrome, or changes in stature similar to the Marfan syndrome.

In our opinion the 2 siblings suffer from a genetic disorder described only in Tunisian Jews, which can best be called the 'brittle cornea syndrome'. This syndrome has 3 major components: spontaneous perforation of cornea (brittle cornea), blue sclera, and red hair. It should be mentioned that red hair is very uncommon in Tunisian Jews and seems to be a 'marker' of the brittle cornea syndrome.

From the family presented here, and the family reported previously⁴ it is evident that this disorder is transmitted as an autosomal recessive trait. The three traits of brittle cornea, blue sclera, and red hair are transmitted by a single gene. All reported homozygotes presented the complete syndrome.

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Diffuse melanoma of the choroid

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SUMMARY An 81-year-old woman with good vision was followed up with the diagnosis of a minimally active melanoma. This tumour was eventually found to be a diffuse melanoma with extraocular extension. Diffuse melanomas of the uvea are difficult to diagnose, have frequent and early extrascleral extension, and have a poorer prognosis than most melanomas of the uveal tract.

Diffuse melanomas of the choroid involve at least 25% of the uveal tract and have minimal elevation (Parsons, 1904). These tumours are particularly treacherous, since they are difficult to diagnose, undergo early and frequent extrascleral extension, and have a higher incidence of metastatic disease than most other forms of choroidal melanoma (Reese and Howard, 1967; Font *et al.*, 1968).

In some ocular oncology centres serial examinations without intervention are performed on patients with slightly raised pigmented choroidal mass lesions until growth is detected (Char and Hogan, 1977; Shields, 1977; Char, 1978). We present a report on a patient suspected of having either a large choroidal naevus or a choroidal melanoma. When growth was detected, the lesion was eventually shown to be diffuse choroidal melanoma with extrascleral extension. This patient presents some of the problems associated with making the correct diagnosis in pigmented choroidal masses, points out the risks of following up such patients, and emphasises the necessity to consider diffuse melanoma in those patients with slightly raised pigmented lesions of large diameter of the uveal tract.

Case report

The patient was an 82-year-old Caucasian female who was initially examined by her local ophthalmologist because of sharp pains of recent onset in the right eye. The patient's systemic and ocular past medical history was essentially normal.

On initial evaluation in the Ocular Oncology

Unit in November 1977 her visual acuity in the right eye was 20/25 (6/7.5). Examination of the anterior segment showed nothing abnormal. Examination of the posterior pole of the eye revealed a pigmented, slightly raised (<2.5 mm) choroidal lesion extending from approximately 5.30 to 8.30 o'clock and involving both the posterior and anterior fundus. There were multiple drusen over the surface of this rounded lesion, without orange pigmentation or subretinal fluid. No scotoma could be demonstrated with either a 1-4-E or a IV-4-E isoptre on Goldmann perimetry.

A fluorescein angiogram was nondiagnostic. The affected area of the choroid showed minimal hyperfluorescence without tumour vessels, hot spots, or subretinal leakage. B-scan ultrasonography showed a tumour mass of approximately 2 mm in elevation with equivocal choroidal excavation.

This lesion was thought to be minimally active choroidal melanoma, and after discussion with the patient it was decided to follow her up with serial examinations.

The lesion appeared to remain stable until about 11 months after the patient's initial visit, when increased elevation was observed on clinical examination. The overall diameter of the lesion was unchanged, but in its central portion a relatively nonpigmented mass was noted to be approximately 5 mm in elevation. Examination of this lesion by ultrasonography and computerised tomography suggested extraocular extension (Figs. 1 and 2). A radioactive phosphorus uptake test was strongly positive, and during the performance of this test a large extrascleral extension was observed which arose from the posterior, nonelevated portion of

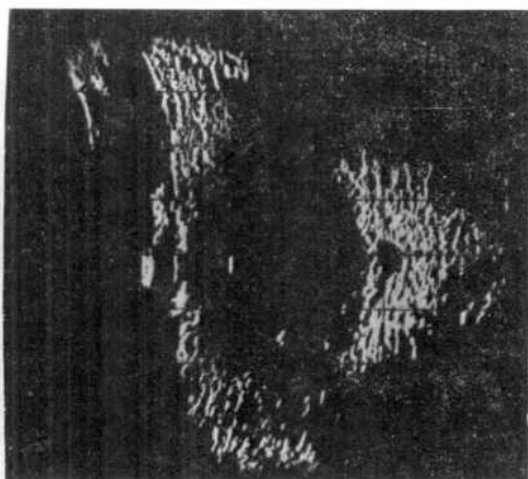


Fig. 1 CT scan showing extraocular extension

the tumour mass. An extensive search for metastases was negative, and an orbital exenteration was performed 2 days later.

Microscopic examination showed a flat diffuse tumour extending from the ciliary body to the posterior pole, equal to approximately 1/3 the circumference of the globe (Fig. 3). The tumour was composed primarily of large, bizarre epithelioid cells; there was no break through Bruch's membrane. Near the posterior margin of the tumour distant from the area of elevation observed clinically there was an extrascleral extension.

The patient has done well, without evidence of metastatic disease, in the 12 months since surgery.

Discussion

Fuchs (1882) described diffuse malignant melanomas of the uveal tract. Since then approximately 130 patients with diffuse melanomas have been reported (Fuchs, 1882; Ewetzky, 1898; Kipp, 1903-05; Parsons, 1904; Cargill and Mayou, 1907; Alexander and Shea, 1964; Reese and Howard, 1967; Spaulding *et al.*, 1967; Font *et al.*, 1968; Machemer, 1968). Font *et al.* (1968) have enumerated criteria for the diagnosis of diffuse melanoma: involvement of at least 1/3 of the uveal tract; tumour thickness between 3 and 7 mm in height; and involvement of the posterior uvea if the main tumour is in the iris or pars plicata.

Diffuse melanomas of the uveal tract are difficult to diagnose. Font *et al.* (1968) reported that 40% of their cases were not considered to have tumours before enucleation. Often the presentation of these tumours may simulate absolute glaucoma, uveitis, or recurrent scleritis. In the present case none of

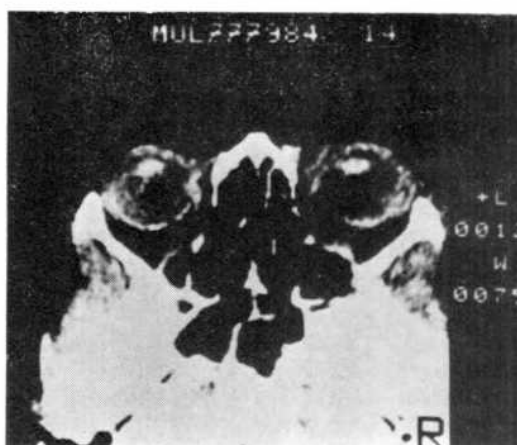


Fig. 2 B-scan ultrasound showing extraocular extension of a choroidal melanoma

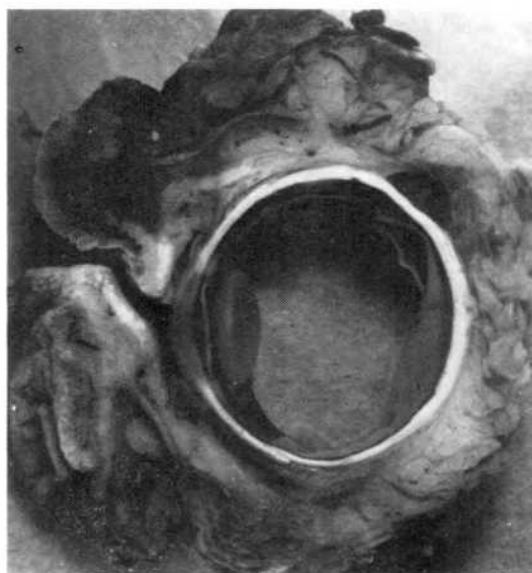


Fig. 3 Exenteration specimen showing extraocular extension of the diffuse melanoma

these findings was observed, and the patient's visual acuity was excellent. Reese and Howard (1967) described the typical diffuse choroidal melanoma as having surface drusen and finger-like projections; neither of these signs clearly differentiates a choroidal naevus from this malignant tumour. The vast majority of choroidal naevi are less than 6 mm in diameter and 1.5 mm in height; in lesions larger than this the possibility of a diffuse melanoma should be raised (Gass, 1977). While we have abandoned the routine use of the radioactive phosphorus uptake test in the evaluation of chori-

dal melanoma patients, perhaps in this group of subjects, those with minimally raised large pigmented choroidal lesions, it may be useful (Reese and Howard, 1967). In the present case, and 2 patients reported by Reese and Howard (1967), the radioactive phosphorus uptake results were strongly positive. However, in other cases of diffuse and localised choroidal melanomas false negative and false positive results have been observed (Alexander and Shea, 1964; Zakov *et al.*, 1978).

It is important to make the correct diagnosis early in diffuse melanoma. Between 39 and 53% of patients with this form of uveal melanoma had extraocular extension versus 13% in a large series of unselected patients with choroidal melanomas (Starr and Zimmerman, 1962; Reese and Howard, 1967; Font *et al.*, 1968). These patients tend to have a generally more malignant cell type on histological examination and a lower survival rate than most other types of choroidal melanoma (Font *et al.*, 1968).

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Antibodies to skeletal muscle actin and their reactivity with malignant melanoma of the choroid

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SUMMARY Imprints of choroidal malignant melanoma cells were treated with serum containing antibodies to a purified preparation of actin derived from skeletal muscle. Evidence of a positive reaction, as shown by indirect immunofluorescence, substantiated an impression based on morphological criteria that choroidal melanoma cells contain actin protein. The significance of this protein in tumour biology is discussed, and a possible interference by antiactin antibodies in the immunodiagnosis of choroidal melanoma is highlighted.

Actin is a globular contractile protein with a molecular weight of about 48 000. Together with myosin it plays a fundamental role in muscular contraction.

Skeletal muscle fibres are composed of a macromolecular complex of polymerised actin and myosin organised into interdigitating filaments which are able to slide over one another. The interdigitations are responsible for the characteristic banded pattern of skeletal muscle fibres. Smooth muscle fibres similarly contain actin and myosin, which may, however, be present either in filamentous (F actin) or soluble globular forms (G actin). Furthermore the filaments do not have the banded spatial arrangement of striated muscle but can lie either parallel or at right angles to each other.

Recent studies¹⁻⁴ show that actin, although principally found in muscle fibres, is present in almost all eukaryotic cells, where it can be demonstrated in at least 2 forms: as bundles of filaments or as a randomly orientated meshwork of filaments.⁵ Apart from providing structural support (cytoskeleton), the contractile proteins take part in other mechanicochemical activities of the cell such as cell movement and mitotic division.

The presence of actin in cells which normally display only limited mobility suggests that it performs functions additional to those required in cell movement, such as endocytosis, exocytosis, cell division, and in-vitro attachment to glass surfaces in tissue culture.^{4,6-8}

The content and molecular organisation of actin

varies in different types of cells as well as being modified by the physiological state of the cell.⁹⁻¹¹

It has been shown that actin is present in large amounts in malignant tumours arising from some epithelial tissues,⁹ thus implying a possible role in the invasive properties of a malignant tumour. Whether this is true of cancers in general and of malignant melanoma of the choroid in particular is not known. A striking feature of actin in non-muscle cells is that it aggregates into filaments which can change their pattern and appearance in a matter of hours.¹¹ Although some of these changes have been noted in pathological tissues,⁹ they have not been studied in detail, and their significance is largely obscure.

Antibodies reacting with smooth muscle antigens were first described in patients with chronic active hepatitis.¹² The smooth muscle antibodies (SMA) in such sera were subsequently shown to react with nonmuscle tissues, including the endothelial cells of renal glomeruli,¹³ hepatocytes,^{13,14,15} thyroid cells,^{16,17} fibroblasts,^{18,19} and platelets.^{20,21} All these cell types are now known to contain microfilaments which morphologically resemble the actin filaments seen in muscle tissue. Similar antibodies are now known to occur in the sera of patients with other inflammatory conditions such as cytomegalovirus infection,²² mycoplasma pneumoniae infection,²³ infectious mononucleosis,²⁴ acute and chronic hepatitis,^{25,26} and uveitis.²⁷ They are also a feature of a variety of neoplastic states which include basal and squamous cell carcinomas,⁹ Burkitt's lymphoma, nasopharyngeal carcinoma,^{28,29} carcinoma of the breast,³⁰ and malignant melanoma of the skin.^{9,31}

In a previous communication, using an indirect

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immunofluorescence test, we showed that sera from patients with a variety of inflammatory eye diseases may similarly contain smooth muscle antibodies.²⁷ These sera produced equally strong cytoplasmic fluorescence when tested against choroidal melanoma cell impressions,³² which led us to examine the tumour cells for the presence of contractile proteins.

In an ultrastructural study we showed the presence of varying numbers of microfilaments in the cytoplasm of cells from a single malignant choroidal melanoma, but more recently we have demonstrated them in 21 of 22 similar tumours. These microfilaments, ranging in diameter between 5 and 7 nm, were arranged in loose bundles and aligned essentially parallel to the surfaces of the cells, and were consistent morphologically with actin.³²

In the present communication we describe the reactivity of melanoma cells with antibodies specifically raised against pure actin. This study proves for the first time that choroidal melanoma cells contain actin protein comparable to that found in contractile organs.

Methods and materials

Actin was extracted from the skeletal muscle of an albino rabbit. Initially a crude extract was obtained by a method essentially similar to that described by Iyengar and Weber.³³ Finely minced muscle tissue was soaked in 50% glycerol containing 0.1 M KCl and 1 mM $MgCl_2$ at pH 7 for 3 days. The suspension was filtered and squeezed to remove all the soluble components. The residue was then soaked in a solution containing 0.6 M KCl and 1 mM adenosine triphosphate in distilled water at pH 6.4 for 24 hours. The insoluble residue obtained after filtration was then treated for 2 successive periods of 30 minutes each in 0.3 M KCl at pH 7 and 0.1 M KCl at pH 9 respectively. Finally the residue was treated 4 times with distilled water at pH 9. The final residue was dehydrated in acetone and dried overnight. All procedures were carried out in the cold room at a temperature of 4°C.

PURIFICATION OF ACTIN

The dried powder thus obtained contained actin which was further purified using the aggregation-disaggregation principle.³⁴

Actin was extracted from the acetone-dried powder by suspending it in ice-cooled Tris buffer (2 mM Tris HCl (hydroxymethyl methylamine hydrochloride) 0.2 mM ATP, 0.5 mM mercaptoethanol and 0.2 mM $CaCl_2$ at pH 8) for 30 minutes. The solution was passed through a coarse sintered glass funnel, and the filtrate was further cleared by

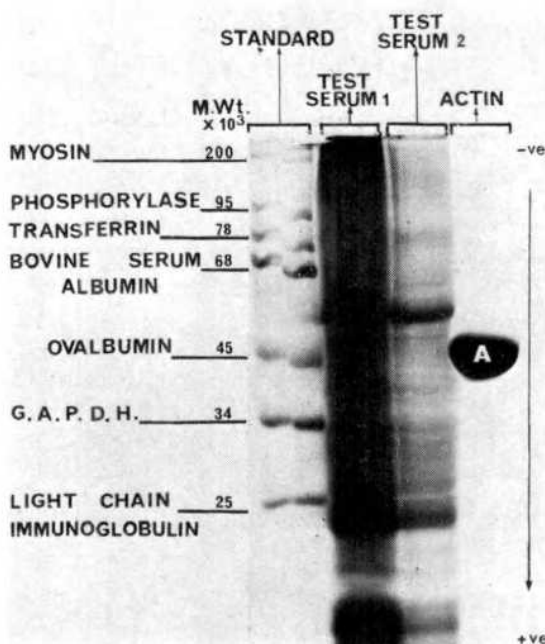


Fig. 1 SDS polyacrylamide gel electrophoresis of the purified actin protein preparation. To provide a scale against which to assess the molecular weight of the test preparation, protein standards of known composition were run in parallel. The resultant mobility of the muscle extract indicated a single component (A) with a molecular weight of approximately 40 000–48 000, which compares with the reported size of 48 000 for pure actin. (Sera from 2 patients run at the same time are irrelevant to the present study and should be ignored.) GAPDH = glyceraldehyde-3-phosphate dehydrogenase.

centrifugation at 10 000 g for 1 hour. To this supernate KCl and $MgCl_2$ were added to give a final concentration of 50 mM KCl and 2 mM $MgCl_2$. The solution was kept on ice for 2 hours in order to polymerise the actin (F actin). More KCl was then added to the solution to bring its concentration to 0.6 M and left for 90 minutes. The solution was centrifuged for 3 hours at 80 000 g, and the resulting actin protein pellet was resuspended in buffer and dialysed with vigorous stirring for 3 days at 4°C, changing to fresh buffer every 24 hours.

The protein concentration in the final solution was measured using a modification of the Lowry technique.³⁵

Identification of actin and the assessment of its purity was carried out by sodium dodecyl sulphate polyacrylamide gel electrophoresis.^{36,37} Pure actin protein (obtained by the courtesy of Dr M. Owen,

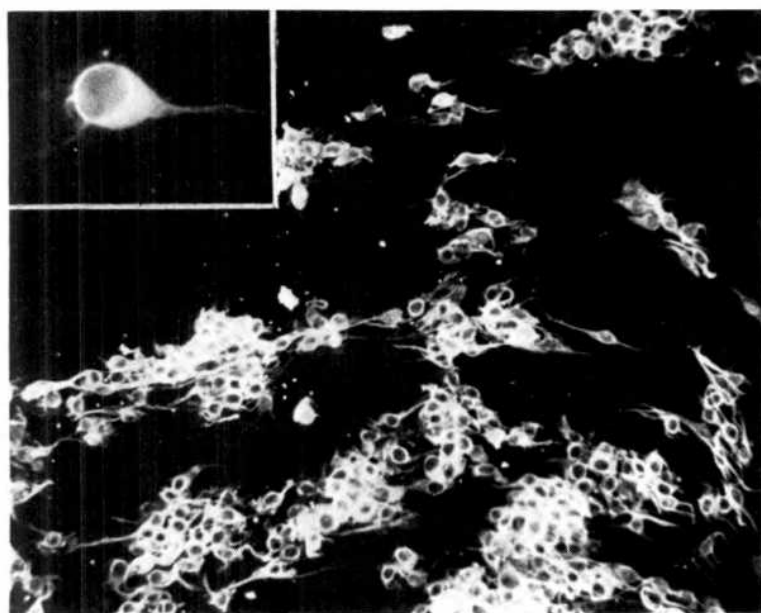


Fig. 2 Indirect immunofluorescence staining of choroidal malignant melanoma cell imprints treated with antiactin antibodies. The bright cytoplasmic fluorescence is indicative of the presence of actin protein ($\times 135$; inset $\times 450$).

National Institute for Medical Research, Mill Hill, London) and other standard proteins of known molecular weight were used as markers. The protein bands in the gel were fixed overnight in 50% trichloroacetic acid and then stained with 0.1% Coomassie brilliant blue solution.

Actin solution was allowed to 'age' by storing for one week at 4°C, to increase its antigenicity,³ and then lyophilised for storage at -20°C.

PREPARATION OF ANTISERUM

Albino rabbits were used to raise antiactin antibodies. Before immunisation the serum of each animal was tested for the presence of antibodies to smooth muscle and other autoantibodies by the conventional immunofluorescence test,³ and only the animals whose sera gave negative results were used.

Each animal received 1 mg of 'aged' actin redissolved in 0.25 ml of distilled water and emulsified with an equal volume of Freund's complete adjuvant (Difco Laboratories). The dose was divided between intramuscular and intraperitoneal injections. The animals were bled after 3 weeks and a booster injection was given. Three weeks later the animals were bled again.

STANDARDISATION PROCEDURE

The antisera thus raised were tested for the presence of antiactin antibodies by a standard indirect immunofluorescence test using frozen sections of a composite block consisting of portions of liver, kidney, skeletal muscle, stomach and salivary gland

from a rat. Fluorescein labelled antirabbit immunoglobulin was obtained from Nordic Diagnostic and the sections were examined under a Zeiss epifluorescence microscope equipped with an FITC interference filter.

Control studies were carried out by using sera obtained from animals prior to immunisation as well as antiactin sera absorbed with purified actin.

REACTIVITY WITH CHOROIDAL MALIGNANT MELANOMA CELLS

Eyes with choroidal malignant melanomas were opened as soon as possible after enucleation (up to a maximum of 5 hours), and the cut surface of the tumour was pressed against multispot slides to give a monolayer of tumour cell imprints. The slides were snap frozen and stored in liquid nitrogen for further use. Cell impressions from 8 different choroidal melanomas were used in this study to test for the presence of actin in tumour cells.

Results

The purity of the actin protein preparation was assessed by sodium dodecyl sulphate polyacrylamide gel electrophoresis (Fig. 1).

The presence of antiactin antibody in the rabbit sera was confirmed by the immunofluorescent staining patterns obtained when the sera were tested against the smooth muscle cells of the blood vessel wall, the muscularis mucosae and smooth muscle fibres between the glands of the stomach,



Fig. 3 Indirect immunofluorescence staining of a single malignant melanoma cell in culture preparation treated with antiactin antibodies. The pattern of staining suggests that the filamentous form of actin is present in the cytoplasm ($\times 567$).

the myoepithelial cells of the parotid gland, liver cells in the region of the cell membranes (polygonal staining pattern), and the actin-containing I bands of skeletal muscle.^{38,39} In each case the staining pattern corresponded to that reported by Trenchev *et al.*³ using antiactin antibodies.

The antiactin sera gave strong cytoplasmic fluorescence with all 8 choroidal malignant melanoma cell impressions. As well as diffuse fluorescence of the cytoplasm, filamentous fluorescence was also observed in the region of the cell processes (Figs. 2 and 3).

The patterns of staining described above were diminished when the sera were absorbed against actin prior to testing, the reduction being most marked when the sera were tested in high dilutions.

Discussion

In an earlier study we reported the presence of intracytoplasmic microfilaments of 4–7 nm diameter in choroidal malignant melanoma cells and suggested that these filaments were probably actin.³² It was also speculated then that the 'false' positive immunofluorescence obtained by testing the sera of patients with nonmalignant eye diseases against the cells of a malignant melanoma might be due to the smooth muscle antibody demonstrated in the serum of these patients.⁴⁰

In the present study by subjecting the melanoma cells to an antiserum raised against a known purified preparation of actin we have been able to demonstrate with some certainty that choroidal malignant melanoma cells contain actin protein. Moreover,

since the pattern of immunofluorescence assumed filamentous and diffuse forms, it is reasonable to suppose that the actin was present in either a filamentous or a depolymerised globular state.

The present study reinforces our claim that the results of immunological tests for the diagnosis of choroidal melanoma based on reactions between patient's serum and preparations of uveal melanoma cells need to be interpreted with circumspection. This is not to say that antibodies to tumour-specific antigens are not a feature of patients with uveal malignancy but rather to emphasise that before such a claim can be made it is essential to exclude the presence of antibodies to actin and, possibly, other cell components.

The significance of the contractile protein filaments in the tumour cells is unknown, though it is reasonable to speculate that they are related to the motility of the cells and hence to the capacity for infiltration and invasion characteristic of malignant tumours.

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Observations on the ^{32}P uptake test

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SUMMARY The results of the ^{32}P uptake test in the diagnosis of intraocular malignancies is presented. The tests were carried out with the use of a newly developed eye probe. A quantitative comparison of different control sites is described, and a statistical analysis has been conducted on the counts obtained during the uptake procedure.

Some investigators have questioned the validity of the radioactive phosphorus (^{32}P) uptake test in the diagnosis of intraocular malignancies because of the presence of false negative or false positive results.¹⁻³ However, its usefulness has been demonstrated by the publication of large series with success rates of 96% and over.⁴⁻⁷

The basis of the test is that neoplastic tissue has an increased rate of phosphate uptake and retains the isotope longer than non-neoplastic tissue. Care must be exercised both in the performance of the test and in the interpretation of the results. To this end published papers which indicate the usefulness of the test also emphasise some relevant practical considerations.

The aims of the present paper are (1) to report on the authors' experience with the ^{32}P test, (2) to assess an experimental eye probe, (3) to describe a quantitative comparison of different control sites,

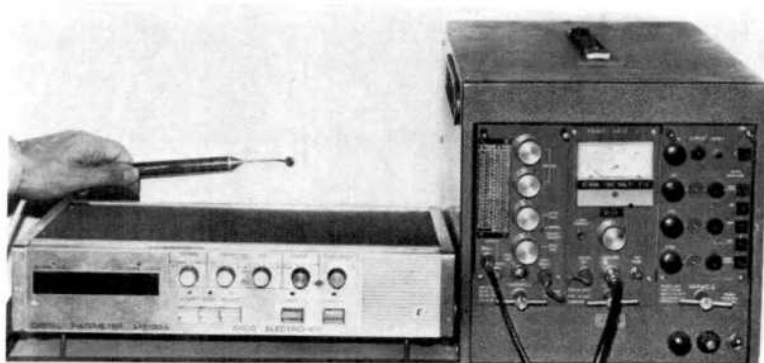
and (4) to conduct a statistical analysis on the counts obtained during the uptake procedure.

Materials and method

The present investigation was carried out with a beta-sensitive semiconductor detector developed at the Instrumentation and Applied Physics Division, Atomic Energy Research Establishment, Harwell, England. The technical details have been published elsewhere.⁸ The detector is a planar, thermally diffused p-n junction, with a diameter of 8 mm, a thickness of 0.5 mm, and a particle window of 50 μm (0.002 in) thickness stainless steel. At an operating bias of 100 volts the depletion depth is 300 μm to 500 μm and the capacitance is approximately 8 pF. The preamplifier is contained within the handle for optimum signal to noise characteristics. The probe was connected to a modified J. and P. 65/063 power unit and 95/2151 amplifier and from there to a digital display (Fig. 1). (An electronic system is now available from Harwell to use with these probes.) The sensitivity of the instru-

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Fig. 1 The semiconductor eye probe with the amplifier and digital display used in the present investigation.



ment is 0.6 counts/s/nCi/ml at 70 volts bias, which is the voltage rating at which the instrument was operated.

In patients to be tested eight μCi of disodium ^{32}P phosphate per kg body weight up to a maximum dose of 500 μCi , was injected intravenously in 5 ml saline. Counts were taken at 24 and 48 hours after injection. The probe was positioned on the sclera over the site of the lesion with minimal pressure, and 2 separate 100 second counts were recorded. The mean of these 2 values was taken as the measured test count. For lesions which were otherwise inaccessible the conjunctiva was usually incised to facilitate accurate localisation of the probe. Counts were also taken over 2 separate control sites. One of these was from a site in the other eye corresponding to the position of the lesion in the fellow eye, and the other was a site in the same eye diametrically opposite the lesion. 100 second counts were taken from each area in turn and then repeated. A mean count of the 4 readings was usually used as the control value.

Before a centre can establish its own criteria for positivity it is necessary to gain experience with the test. Initially, therefore, a 60% increase in counts over the lesion as compared with the control site⁹ was considered positive. When a lesion failed to produce a difference of this magnitude, a careful scan was carried out by moving the probe in relation to the lesion and taking a series of 10 second counts during the process. If an active area was located by this method, 10 consecutive 10 second counts from this area were summed.

The ^{32}P uptake is defined by the equation^{9,10}:

$$U = \frac{T-C}{C} \times 100$$

where U = ^{32}P uptake, T = average counts at test site, C = average counts at control site.

Results

The test was performed on 46 patients. Three patients had a lesion in the iris, while in the remaining 43 patients the lesion was posteriorly situated.

Of the 43 posteriorly placed lesions the majority (33) had the clinical features of malignant melanoma of the choroid, as assessed by ophthalmoscopy, tests of visual function, fluorescein angiography, and ultrasound. In line with current practice some of the smaller malignant melanomas were kept under observation, so that histological confirmation of the diagnosis was made in only 25 cases. Ten cases were considered to have benign lesions. These included 2 lesions removed by local choroidectomy and shown histologically to be benign adenomas,

2 benign naevi, 2 annular serous choroidal detachments, 1 choroidal haemorrhage, 1 retinal and choroidal detachment, 1 serous retinal detachment, and 1 retinoschisis.

With the exclusion of results from iris lesions, since they have been shown elsewhere^{7,9} to be inaccurate and are no longer routinely measured at this centre, results from 2 eyes showing a severe inflammatory reaction which was thought to invalidate the test, and results from 4 posteriorly placed lesions where incision of the conjunctiva was considered to be inappropriate, there were 37 cases available for evaluation of the test. The results in these 37 cases are shown graphically in Fig. 2.

At 24 hours there was considerable overlap

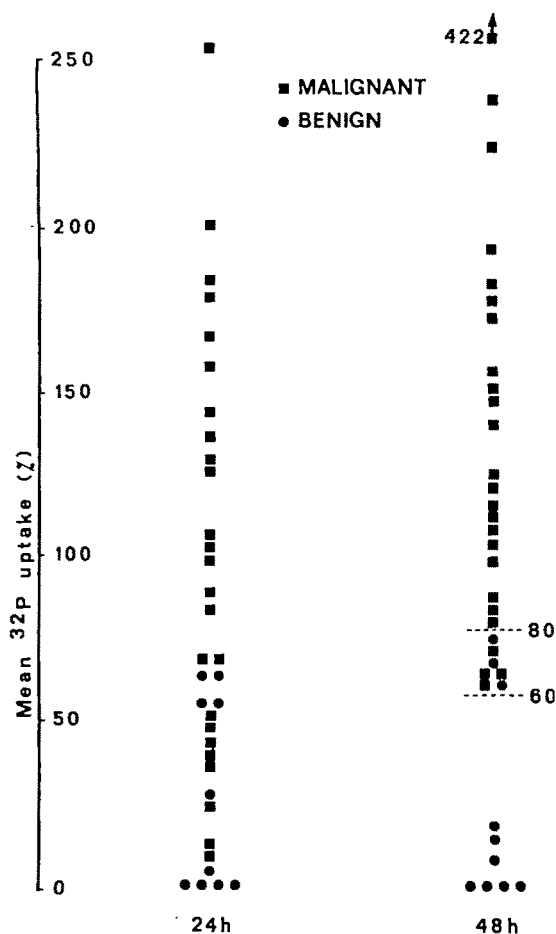


Fig. 2 The mean ^{32}P uptakes obtained at 24 h and 48 h after administration of the isotope. Results are from histologically verified or clinically diagnosed malignant and benign lesions. Thirty-one of the 37 cases plotted had the test performed both at 24 h and at 48 h. The 60% and 80% uptake levels are shown at 48 h.

between counts from benign and malignant lesions, all of the benign lesions and 10 of the malignant lesions (40%) having uptakes of less than 80%.

At 48 hours the separation of the 2 groups was much clearer, 21 of the malignant lesions (84%) having uptakes in excess of 80%, while all of the benign lesions had counts which were less than 80% above control values. In 7 of the 10 benign lesions counts were within 20% of control values, but in 2 benign adenomas and 1 serous choroidal detachment uptakes lay in the range 60–80%. Similarly, 4 of the 25 malignant lesions gave results which lay within this same range.

The mean count in 100 seconds from all the test eyes was 1202 ± 697 (SD) compared with 836 ± 430 for control sites in the affected eye and 693 ± 377 for control sites in the fellow eye. The values of mean uptake using a control site in the affected eye as compared with a control site in the fellow eye are shown in Table 1. At 24 hours there was a 29% difference in the mean uptake derived from these 2 control sites, and at 48 hours the difference was 40%.

The change in uptake between the 24 and 48 hour measurement was also assessed in both groups of patients by placing the test results into 1 of 3 categories (Fig. 3). There were 2 benign and 2 malignant lesions in which the 48 hour uptake was less than the 24 hour uptake by at least 10%. Five benign and 5 malignant lesions had uptakes which were within 10% at the 2 times. While there were only 3 benign lesions in which the 48 hour uptake was greater than the 24 hour uptake by at least 10%, 14 malignant lesions came into this category.

Discussion

When the test was first reported,¹¹ its reliability was limited by the difficulty in siting early detectors accurately over the lesion being investigated. Initially, counting relied on Geiger-Müller tubes which were relatively large and only suitable for anteriorly placed lesions. Smaller Geiger-Müller tubes are now available which may be used for posterior lesions. The recent development of semi-

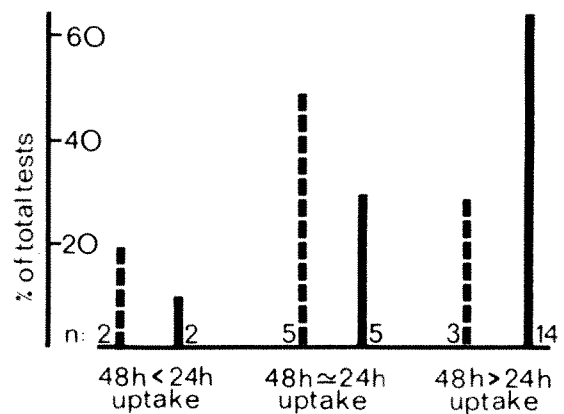


Fig. 3 The % distribution of benign lesions (dashed line) and malignant lesions (continuous line) according to whether the 48 h uptake was less than the 24 h uptake by at least 10%, whether the uptakes at both times were within 10%, or whether the 48 h uptake was greater than the 24 h uptake by more than 10%. Also shown are the actual number of tests in each category.

conductor probes such as that used in the present study have improved the reliability of the ^{32}P test, since these probes are particularly well suited as ocular detectors, being smaller, more sensitive, and more robust than Geiger-Müller tubes.

The experimental probe used in this study has proved to be reliable in use and has withstood ethylene oxide sterilisation at 55°C. Moreover, its high counting efficiency has helped to improve the accuracy of the test.

Measured counts of ^{32}P , both at 24 hours and at 48 hours after injection, greater than 80% above mean control values were all from histologically proved or clinically diagnosed malignant melanomas. At 24 hours after injection there was a significant overlap of results from benign and malignant lesions. At 48 hours there was a clearer separation of the 2 groups in that all lesions with uptakes less than 60% were clinically benign. Lesions giving uptakes between 60 and 80% above control values included 3 benign and 4 out of 25 malignancies.

Thus at both 24 hours and 48 hours an 80% increase in uptake over control values is a strong indication of malignancy, while in addition at 48 hours a count of less than 60% above control counts strongly suggested a benign lesion. Counts between 60 and 80% above control values are equivocal.

The technique of 'scanning' the lesion with the probe to find the area of maximum activity and taking a succession of 10 second counts from this area helps to prevent false negatives. The taking of 10 consecutive 10 second counts enables the operator to detect any slight movement of the probe

Table 1 Mean ^{32}P uptake $\pm$ SEM obtained at 24 h and 48 h with a control site either in the affected eye or in the fellow eye

	Mean ^{32}P uptake $\pm$ SEM	
	Control site in affected eye	Control site in fellow eye
24 h	60 $\pm$ 9	80 $\pm$ 11
48 h	77 $\pm$ 11	115 $\pm$ 17

producing a fall in count. A small or inaccessible lesion or one which is not most active at its centre might otherwise be missed, and it is believed that the modified procedure reported here may help to reduce the possibility of obtaining false negative results in such cases. In some instances scanning did reveal positive uptakes which were lost during the initial 100 second count. In no case was there a comparable increase on scanning the control areas. It is to be emphasised that only consecutive counts were used in arriving at uptake values.

On examining the results from eyes with benign lesions it is apparent that the uptake values in these cases lay in 2 separate groups, those between 0 and 20% above control values, which could well be due to chance, and those in the 60–80% band, which indicated that the lesions were absorbing phosphorus at a similar level to some malignant melanomas. The 2 benign adenomas are interesting in relation to this. Two other such cases have been published in which the ^{32}P test has been performed and where in each case an uptake in excess of 60% was achieved (Table 2).

CHOICE OF CONTROL SITE

As first described, the test was performed with a control site in the fellow eye.¹¹ More recently, however, the trend has been towards using a control site or sites in the affected eye, because a generalised inflammatory reaction in the affected eye might yield a false positive result if a control site in the other eye were used for comparison.¹² There has as yet been no quantitative comparison between these alternative control sites except that carried out by Van Dijk on 11 patients.⁶ The results in Table 1 show that there is a difference in the uptake when different eyes serve as controls, and this difference increases from 24 hours to 48 hours. On average there are fewer counts at the control site in the fellow eye than in the affected eye. There may be at least 2 explanations for this. As well as the possible effect of a generalised inflammatory response in the affected eye there is also the possibility that the probe at the control site in the same

eye is detecting counts from the lesion itself, for although the mean range of β particles from ^{32}P is 3 mm the maximum range is 7 to 8 mm. The raised count at a control site in the same eye from this latter cause might obscure the difference between control and test counts and lead to a false negative result. Because the use of a control site in the fellow eye might, as already explained, lead to a false positive result, in the uptakes quoted in the present paper a mean control count from sites in both eyes was used.

REPEATABILITY

On each occasion two measurements were taken at ostensibly the same site. The scatter in the differences between these 2 values is a result of 2 factors. One is due to the Poisson distribution, which is a feature of all radioactive decay processes; this is a counting error. The other may be termed a positioning or location error resulting from the impossibility of placing a probe in exactly the same position for the 2 successive counts. It may be shown that for the mean counts obtained the standard deviation of the difference in 2 counts on the basis of the counting error alone is 4% for the test counts, 5% for control sites in the same eye, and 5% for control sites in the fellow eye. Although the most probable value of the difference in the 2 readings at the same site is zero, the mean value of the difference with regard to the counting error is the standard deviation of the difference, i.e., 4 to 5%. The mean values of the differences actually obtained were 12% for the test counts, 13% for the control sites in the same eye, and 14% for control sites in the fellow eye. The difference between the total error and the counting error, some 8%, is the positioning error, and this is relatively constant for the three different counting locations.

Conclusion

Carefully used, the ^{32}P test employing the solid state detector described in this paper is capable of distinguishing clearly between the majority of benign and malignant intraocular lesions. Two benign adenomas and 1 case of serous detachment of the choroid investigated showed accumulation of ^{32}P similar to that encountered in a minority of malignant melanomas. The majority of malignant tumours, however, showed uptakes in excess of 80% of control values, a level which was reached by none of the benign cases.

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Table 2 A comparison ^{32}P uptake values in cases of benign adenoma

	^{32}P uptake		
	1 h	24 h	48 h
Goldberg <i>et al.</i> ¹⁰	127	62	60
Jarrett ⁵	—	—	122
Present study, case 1	—	63	75
Present study, case 2	—	65	62

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Changes in visual function and in the posterior segment of the eye during treatment of onchocerciasis with diethylcarbamazine citrate

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SUMMARY Eighteen patients, moderately to heavily infected with onchocerciasis, were treated with a standard course of diethylcarbamazine citrate (DEC-C). In addition to the well recognised systemic reactions to treatment, the following ocular changes occurred during therapy: (1) Transient pigment epithelial lesions were detected in 7 patients by fluorescein angiography. (2) Optic disc leakage, as shown by fluorescein angiography, developed in 9 patients, and increase of pre-existing leakage was demonstrated in 3 further patients. (3) Visual field loss was documented in 5 patients. These observations have grave implications for DEC-C therapy in onchocerciasis. They emphasise the need for great caution in its use in the treatment of onchocerciasis in heavily infected patients and for close supervision of ocular function during therapy.

It is generally agreed that the clinical manifestations of onchocerciasis are related to the presence throughout the body of microfilariae and that the adult worms (macrofilariae) play little part in the production of disease save as a source of microfilariae. Since its introduction over 30 years ago diethylcarbamazine citrate (DEC-C) has been the principal microfilaricide in the treatment of onchocerciasis. It may be used alone or given as an adjunct to suramin, which is used mainly as a macrofilaricide but is also microfilaricidal. It is generally agreed that DEC causes severe systemic reactions during treatment of heavily infected patients, such as dermatitis, lymphadenopathy, headache, and vertigo, and these have been the principal objections to it (Fuglsang and Anderson, 1974; Bryceson *et al.*, 1977). It has been suggested that vision may be seriously impaired, and in particular there is some evidence that optic atrophy may be precipitated by the use of DEC (Anderson *et al.*, 1976a; Anderson and Fuglsang, 1978).

The present study was designed to assess if visual loss and morphological changes in the posterior segment of the eye occur with DEC therapy.

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Patients and methods

The patients were drawn from villages on the Bussere river, near the town of Wau in Bahr el Ghazal Province of Southern Sudan, where moderate to heavy infection with *Onchocerca volvulus* had already been identified by previous survey (Zaroug, Bashir, Fuglsang and Anderson, in preparation). Patients who conformed to the following criteria were invited to join the study: (i) visual acuity of 6/6 with each eye, or, if worse, that the loss was due to disease other than onchocerciasis; (ii) no gross choroidoretinal disease; (iii) visual field loss restricted to arcuate defects; (iv) microfilariae detected in the anterior ocular tissues; (v) clear ocular media.

Eighteen male patients were admitted to an 8-day therapeutic study. Only 4 had received previous treatment for onchocerciasis: patient 1 had injections of suramin in 1969, patient 3 in 1978, patient 7 in 1974, and patient 9 many years previously. Three other male patients were treated with a shorter, more intensive course of DEC-C.

Before the start of treatment a general examination was undertaken, including assessment of nodules. Skin snips were taken from the buttock and near the outer canthus of the eye with a corneoscleral punch, and microfilarial counts were made by standardised techniques (Fuglsang and Anderson, 1977).

Visual acuity was measured at 6 metres by an illiterate 'E' chart, and visual fields were assessed by confrontation. New field defects were identified if loss was detected in a previously intact superior or inferior hemifield. Changes of a pre-existing field defect could not be judged with certainty by this technique and were not recorded as a change. Pupils were tested by the 'swinging flash-light test'.

The number of globular infiltrates (Jones *et al.*, 1978) at the limbus was counted each day by means of a loupe and focal illumination. The anterior segments were examined with a Haag-Streit slit-lamp, and an assessment was made of the number of microfilariae in the anterior chamber and cornea. Colour and fluorescein fundus photography was undertaken with a Kowa RC 2 fundus camera with the pupils dilated. Fluorescein angiograms were recorded on Ilford HP5 film (ASA 400) after intravenous injection of 20% fluorescein sodium.

MANAGEMENT

The patients were admitted to the Military Hospital, Wau, for treatment with DEC-C at a dosage schedule similar to that which has been employed routinely for the treatment of onchocerciasis. The first 18 patients were given 25 mg b.d. on the first day, 50 mg b.d. on the second, 100 mg b.d. on the third, and 150 mg b.d. on the 5 subsequent days, except patient 2, who was given half doses because of his small size (28 kg).

The patients' general status was assessed twice daily, and the level of treatment was reduced if there appeared to be excessive disability as a result of therapy. Skin snips were repeated on the seventh day of treatment. Visual function was recorded and fundus photography repeated on alternate days after the start of treatment. Slit-lamp examination was repeated on the fifth day of treatment.

Results (see Table 1)

PRE-TREATMENT STATUS

General

All 18 patients had palpable nodules in the pelvic region, and patient 12 had 1 on the head. Microfilarial counts at the buttock were over 100 per snip in all but 1 patient and at the outer canthus over 15 in 11.

Ocular

Microfilariae were seen in the cornea of all patients, and in the anterior chamber in all but 3. All but 4 patients had a visual acuity of 6/6 with each eye, and the worst vision recorded was 6/9. In 2 of them minor traumatic corneal scars were present, and in the other 2 no reason for the mild reduction in

acuity was found. In patients 1-9 no visual field loss was detected; patients 10, 11, 13, and 16-18 had arcuate loss in the superior and inferior hemifields of each eye; patients 12 and 14 had one intact hemifield; and patient 15 had field loss in 1 eye only.

Nine patients had normal fundi and angiograms (nos. 2, 4, 7, 8, 10, 12, 14-16), 6 had mild optic disc leakage on angiography (nos. 1, 3, 5, 9, 13, 17), 1 had mild retinal pigment epithelial changes giving rise to transmission defects (no. 6), and 2 had pigment epithelial defects and optic disc leakage (nos. 11, 18).

RESPONSE TO TREATMENT

General

All patients developed itching associated with a papular skin rash which evolved to confluent oedema by the third day of treatment, and which resolved in nearly all patients by the end of the fourth day. Similarly all had early tenderness of the inguinal and axillary lymph nodes, which started to resolve after 4 days of treatment. The severity of these symptoms caused us to reduce the dose during the second day of treatment in patients 2 and 14. In patient 2 vomiting occurred immediately after taking the tablets on the morning of day 3, attenuating further the level of treatment early in his course.

All but 6 patients (nos. 2, 3, 10, 11, 14, and 17) complained of headache, particularly during the first 4 days of treatment, and all but 4 had vertigo (nos. 6, 7, 11, and 14), which had a similar time course to the headache. A few patients had symptoms of upper respiratory tract inflammation and some had gastrointestinal disturbances.

During the second half of the course of treatment arthralgia was the most severe complication, affecting 10 patients (nos. 1, 3, 7, 8, 10-14, and 16), and it was particularly severe in nos. 3, 10, 12, and 14. Most commonly involved were wrist, ankle, elbow, and metatarsophalangeal joints, and some patients complained of backache. In patient 10 the extent of the disability caused us to reduce the dose of DEC-C. Microfilarial skin counts on the seventh day at the buttock were 0 in 10 patients, 1 in 3 and 2-5 in 5, and at the outer canthus 0 in 13, 1 in 4, and 2 in 1.

Ocular

Globular infiltrates at the limbus occurred in all patients during the first day of treatment, and they were seen until the end of the course of DEC-C. There was considerable fluctuation in the number of globular infiltrates from day to day, and the number did not correlate with any other attribute of the patients' response.

Table 1 Clinical manifestation of disease and new lesions acquired during DEC-C therapy

Patients		Pretreatment MF count				VA		Pre-existing lesions		New lesions			
No.	Age	AC	C	OC	B	RE	LE	Field loss	OD leak	Field loss	RPE	OD leak	Arthralgia
1	45	6-20	6-20	144	471	6/6	6/9	-	+	-	-	+	+
2	10	6-20	20-50	137	478	6/6	6/6	-	-	-	+	+	-
3	25	50+	20-50	34	67	6/6	6/6	-	+	+	+	++	++
4	33	1	50-100	48	269	6/6	6/9	-	-	-	+	+	-
5	40	1	50-100	70	190	6/6	6/6	-	+	+	-	+	-
6	18	1	6-20	4	228	6/6	6/6	-	-	-	+	+	-
7	20	0	6-20	2	172	6/6	6/6	-	-	-	-	-	+
8	30	1	6-20	3	257	6/6	6/9	-	-	-	-	+	+
9	45	0	2-5	2	553	6/6	6/6	-	+	-	-	+	-
10	40	1	20-50	43	627	6/6	6/6	+	-	-	-	+	++
11	16	1	6-20	190	119	6/6	6/9	+	+	-	+	++	+
12	25	50+	6-20	120	223	6/6	6/6	+	-	+	+	+	++
13	30	6-20	6-20	1	600	6/6	6/6	+	+	-	-	+	+
14	15	2-5	50-100	20	697	6/6	6/6	+	-	+	-	+	++
15	18	50+	20-50	18	360	6/6	6/6	+	-	+	-	+	-
16	28	0	2-5	16	706	6/6	6/6	+	-	-	-	+	+
17	26	50+	2-5	5	842	6/6	6/6	+	+	-	+	++	-
18	39	1	2-5	11	900+	6/6	6/6	+	+	-	-	+	-
19	31	1	0	8	223	6/18	6/6	-	-	-	-	-	-
20	24	0	20-50	83	500	6/6	6/6	-	+	-	+	++	-
21	32	0	6-20	98	689	6/6	6/60	+	+	-	+	+	-

AC=anterior chamber. C=cornea. OC=outer canthus. B=buttock. OD=optic disc. RPE=retinal pigment epithelium. + = Moderate. ++ = Marked.

At 5 days nearly all the corneal microfilariae were straight, and there was opacification of the surrounding corneal stroma except in patients 7 and 10. In the anterior chamber live microfilariae were seen in patients 2, 4, 5, 12, 15, 17; there was a mild flare in most cases, but no cells were seen.

On day 2 patients 3, 4, 6, 11, 12, and 17 showed discrete retinal pigment epithelial lesions at the posterior pole. They were undetectable by ophthalmoscopy and were demonstrated only by fluorescein angiography. In the dye transit there was no obvious abnormality, but during the subsequent 5 minutes multifocal progressive dye leakage developed into the retinal pigment epithelium, giving rise to multiple small hyperfluorescent spots at the posterior pole (Figs. 1-3). The distribution of these lesions

was not constant, but there was a tendency for them to occur at the edge of the macula region (10-15° from the fovea). In all but patient 6 these lesions had resolved by day 4. On day 4 patient 2 had these multifocal lesions (Fig. 1); it was this patient who had missed 2 doses of DEC-C, so that this did not represent the 4th day of constant therapy. After resolution there were no changes at the site of the previous retinal pigment epithelial lesions in some cases, while there were small transmission defects in others.

Optic disc leakage occurred in one or both eyes in 9 patients (nos. 2, 4, 6, 8, 10, 12, 14-16) in whom there was no dye leakage at the time of the initial study (Figs. 2 and 4), and in 3 (nos. 3, 11, 17) leakage increased when the initial and final studies were

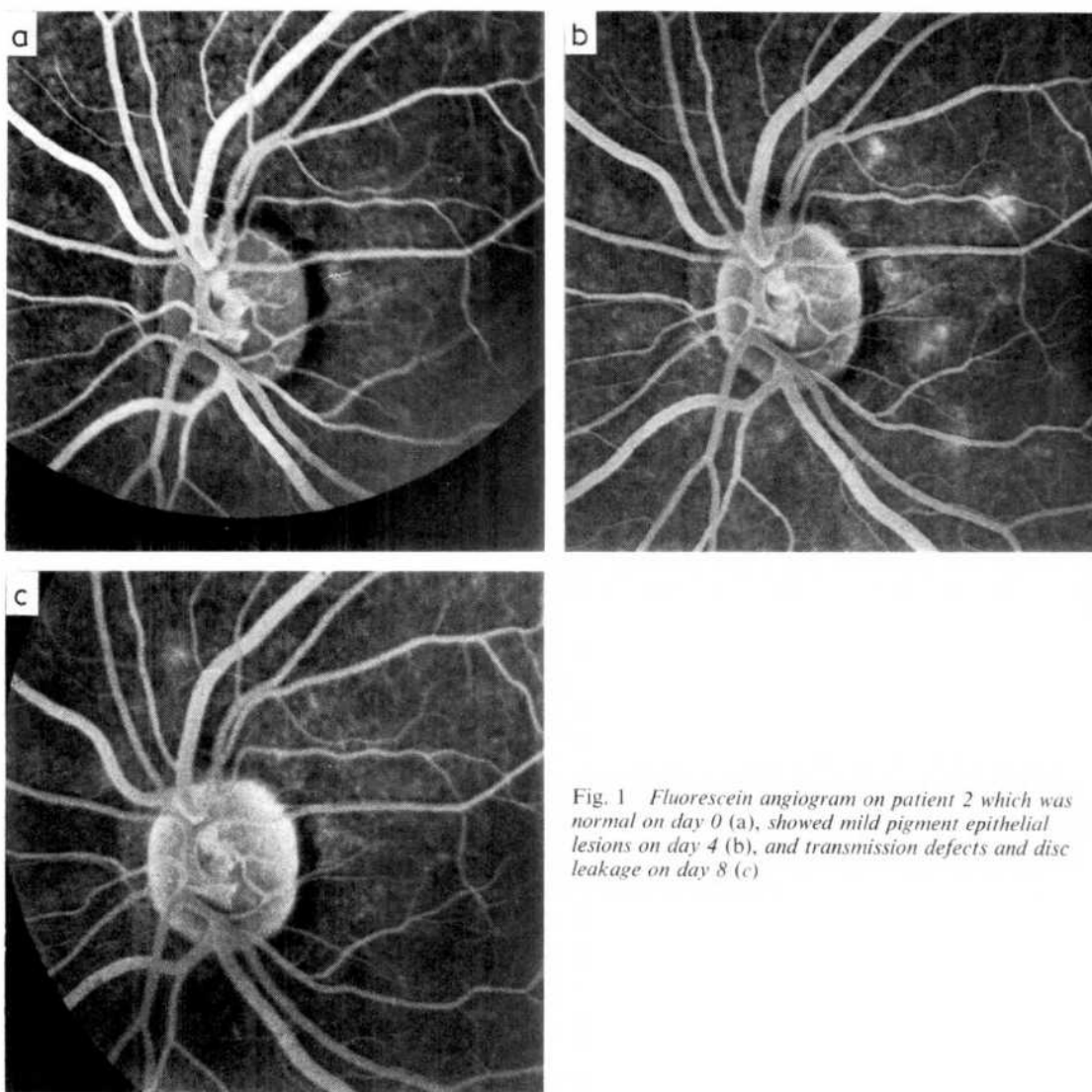


Fig. 1 Fluorescein angiogram on patient 2 which was normal on day 0 (a), showed mild pigment epithelial lesions on day 4 (b), and transmission defects and disc leakage on day 8 (c)

compared. In most patients the leakage progressed during the course of treatment but was confined to the optic disc. Dye leakage into the surrounding neuroretina occurred in only 2 patients (nos. 3, 11) (Fig. 2).

No patient lost visual acuity. In 5 new visual field loss was recorded (nos. 3, 5, 12, 14, and 15) and in patient 3 this occurred in both eyes; this finding was recorded from 2 to 8 days after starting DEC-C. The defects were arcuate and progressed very rapidly, and in patients 3, 12, and 14 nearly a whole hemifield had been lost to hand movements by day 6. At this stage it was considered undesirable to continue DEC-C, and patients 3, 12, 14, and 15

were given betamethasone 6 mg daily for 2 days. The defects were not reversed, even though in patient 15 a defect had been present for no more than 2 days.

SUBSIDIARY STUDY

Three additional patients (nos. 19–21) were admitted for a short trial of DEC-C to observe in more detail the time course of the pigment epithelial lesions. In 2 (nos. 19, 20) there was no evidence of pre-existing ocular damage due to onchocerciasis, though patient 19 had a traumatic corneal scar in the right cornea with reduced acuity. Patient 21 had noticed poor left eye vision in early childhood.

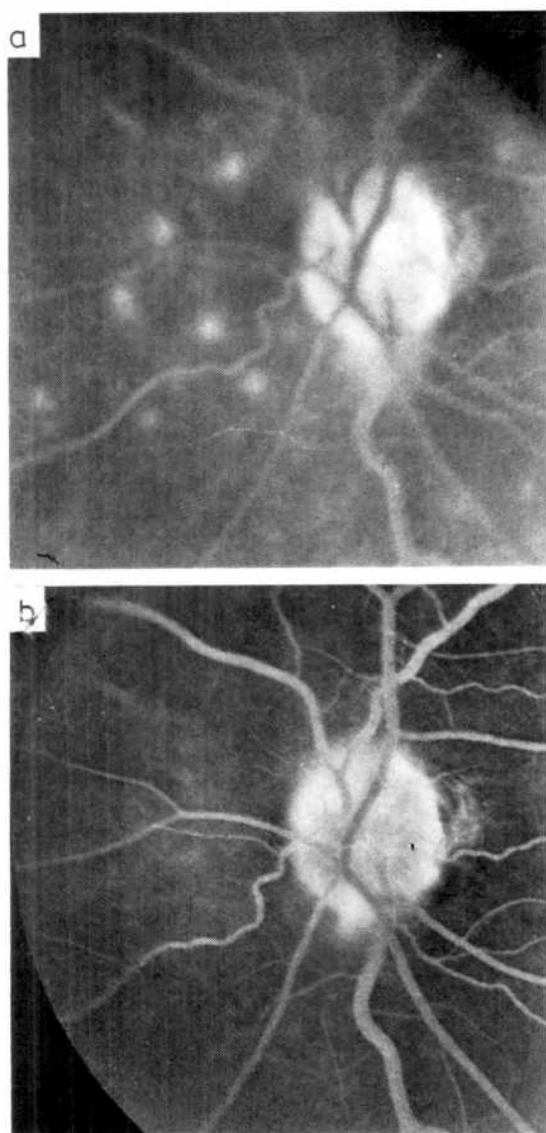


Fig. 2 Fluorescein angiogram on patient 3 showing pigment epithelial lesions around the optic disc leakage on day 2 (a). By day 8 the pigment epithelial lesions had resolved, but the disc leakage persisted and extended into the neuroretina (b)

This eye also had a corneal scar due to trauma, the eye was divergent, and there was evidence of left optic nerve disease in the form of visual field loss and a left relative afferent pupillary defect. Patient 19 had received injections of suramin and DEC tablets 4 years previously for onchocerciasis. All 3 were moderately to heavily infected and had ocular microfilariae.

These patients were given DEC-C 50 mg b.d. on day 1, 100 mg b.d. on day 2, and 150 mg b.d. on day 3. All 3 suffered skin itching, headache, lymph node enlargement, and vertigo. The ocular status was reviewed daily during the 3 days of treatment. Patient 19 had no morphological changes in the fundus during the 3 days of review. Patient 20 developed pigment epithelial lesions on day 1. These had resolved by day 2, by which time new lesions had appeared (Fig. 5); they had all resolved

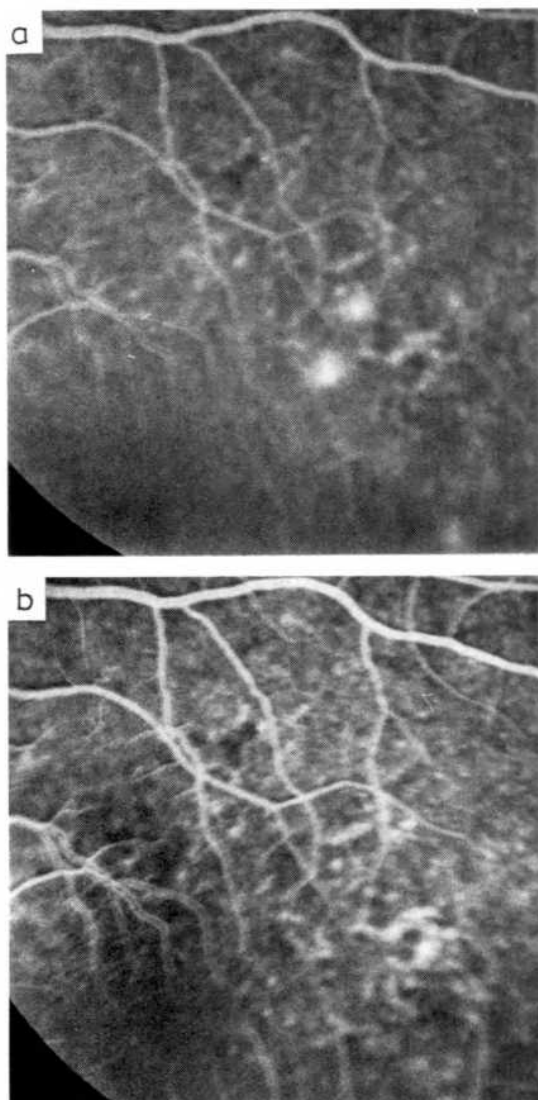


Fig. 3 Patient 11 had pigment epithelial lesions on fluorescein angiography and pre-existing transmission defects on day 2 (a). By day 6 the new pigment epithelial lesions had resolved (b)

by day 3, but dye leakage at the optic disc was recorded at that time. No. 21 had pigment epithelial lesions on day 2 only, and the optic disc leakage increased.

Discussion

Since no control group was used in this study, it could be argued that the changes recorded in these patients occurred by chance and were unrelated to

DEC-C therapy. However, the finding of change in so high a proportion of the patients argues against this view. Patients were selected for study on the basis of availability and were not exceptional when compared with other members of the community in which they lived (Zaroug *et al.*, in preparation), and there is no reason to believe that they were particularly at risk of developing acute posterior segment inflammatory disease. Furthermore, no retinal pigment epithelial disease of the type recorded was seen before the start of therapy, and it was rarely observed in our previous studies (Bird *et al.*, 1976). Similarly, the rapidity of visual field loss that occurred in our patients is unlikely to occur in the untreated disease. Therefore it is likely that the functional and morphological changes recorded were precipitated by DEC-C therapy.

The retinal pigment epithelial changes were short-lived in this group of patients and implied no obvious threat. They were presumably due to a transient injury early in the course of treatment. The time course of recovery is not exceptional for the retinal pigment epithelium, since it was identical to that seen after mild supratherapeutic laser burns (Borland *et al.*, 1978). The injury may have been caused by release of a toxic substance by the dying microfilariae. Alternatively choroidal inflammation may either have affected the pigment epithelium directly or have caused blood flow changes in the choriocapillaris, inducing temporary pigment epithelial ischaemia (Deutman and Lion, 1977; De Laey, 1978).

By contrast the optic nerve disease was sustained and appeared to be the cause of functional changes, since the pattern of visual loss clearly indicated anterior optic nerve disease. All patients with field loss had morphological changes at the optic nerve head, but several patients had disc changes without functional loss. Admittedly the method of testing for field loss was relatively crude, and it was impossible to detect with certainty changes in defects already present in the hemifield. It is possible that more sophisticated techniques would have revealed an even higher incidence of visual morbidity. The nature of the optic disc changes and the field loss resemble those in the untreated disease (Vedy and Sirol, 1971; Bird *et al.*, 1976; Thylefors and Tøjum, 1978). Most authors agree that the optic nerve disease is inflammatory in origin, related to microfilariae which have been identified in the optic nerve (Mira, 1934; Rodger, 1960; Paul and Zimmerman, 1970), the inflammation being precipitated by microfilarial death.

There were no changes in retinal vascular permeability as shown by fluorescein angiography and no white spots beneath the internal limiting

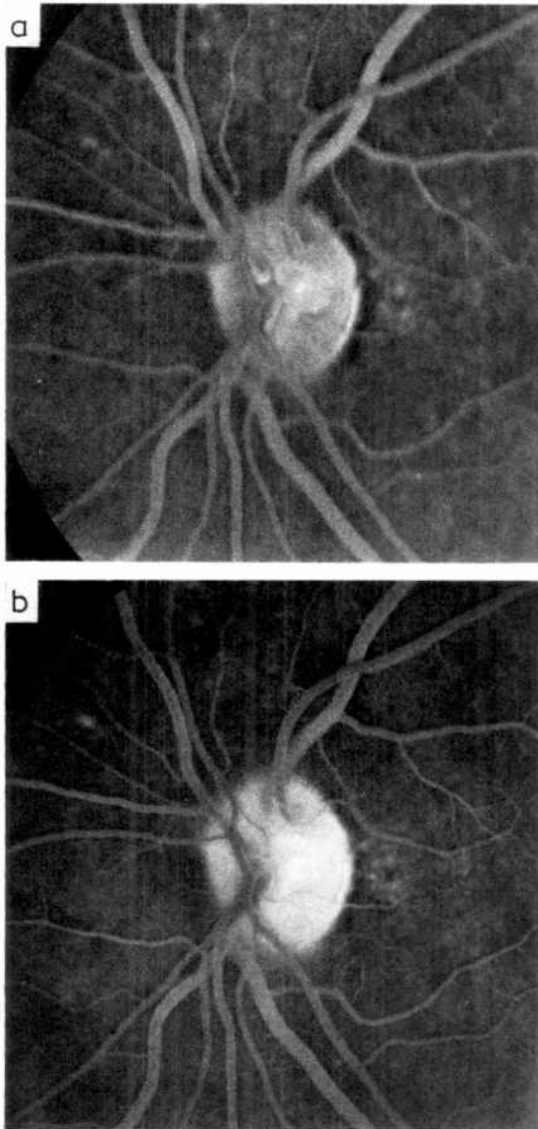


Fig. 4 Fluorescein angiography on patient 6 showing development of optic disc leakage from day 0 (a) to day 6 (b)

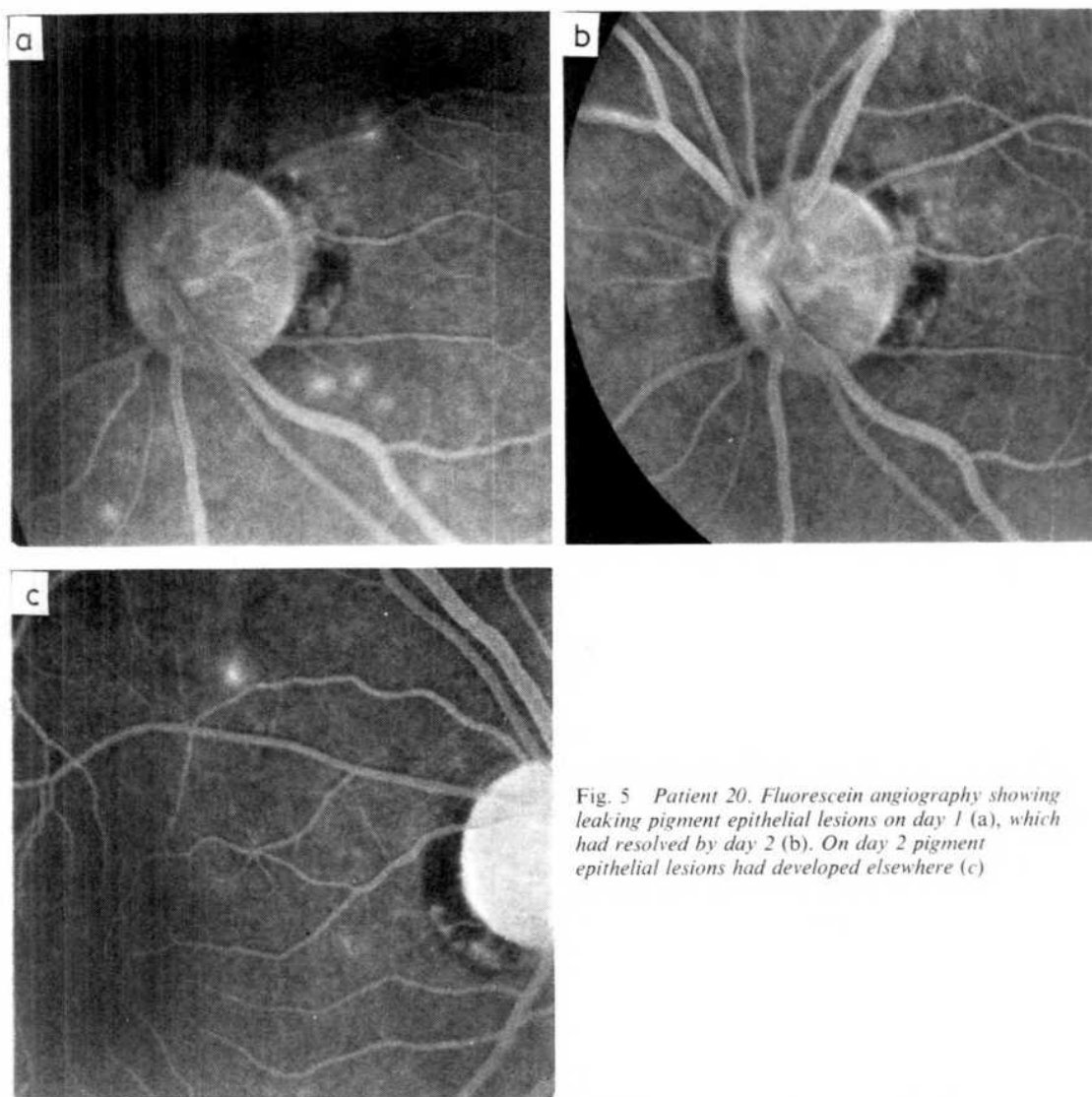


Fig. 5 Patient 20. Fluorescein angiography showing leaking pigment epithelial lesions on day 1 (a), which had resolved by day 2 (b). On day 2 pigment epithelial lesions had developed elsewhere (c)

membrane, as described by Vedy *et al.* (1971). The difference between our observations in Sudan and those in Chad (Vedy *et al.*, 1971) may be related to the differences in the nature of the disease in different countries. Alternatively the lack of retinal changes may be due to a different effect of DEC-C on microfilariae in the choroid and optic nerve on the one hand and in the retina on the other. The presence of live microfilariae in the anterior chamber at a time when all corneal microfilariae were dead, as seen in our patient, would support this explanation.

The risk of posterior segment changes during DEC-C therapy appeared to be greater in patients with high corneal microfilarial counts, which would

not be surprising if the changes detected were caused by dying microfilariae. The apparent correlation of DEC-C induced disease with the density of microfilariae in the ocular tissues would imply that studies on populations with different intensities of infection might provide different results. Patients more heavily infected than those described here may suffer a higher incidence of complications, whereas those more lightly affected may be at no risk from DEC-C therapy.

It was our impression that the most severe arthralgia occurred in those patients with visual field loss. Surprisingly, no other general pretreatment attribute distinguished those patients who suffered functional

loss from the others and, apart from arthralgia, posterior segment inflammatory disease was not associated with any of the other manifestations of DEC-C therapy, such as severity of dermatitis, headache, vertigo, or the number of limbal globular infiltrates.

The number of ocular microfilariae detected did not appear to be the only determinant of posterior segment change leading to visual loss; patient 2 had a large number of microfilariae in the anterior chamber and cornea but had no functional loss, and there was nothing to indicate that he was at less risk than patient 14. Other factors which may have influenced the effect of DEC-C, such as microfilarial mobilisation and immunological responses, were not studied in these patients.

Furthermore the results suggested that retinal pigment epithelial changes do not necessarily imply a threat of optic nerve disease and that optic nerve disease may occur in the patients without previously detected pigment epithelial changes. However, observations on patients 19–21 indicate that pigment epithelial changes may have resolved in some patients by day 2 at the time of the first review.

It is possible only to speculate on the pathogenetic relationship between DEC-C therapy and the changes recorded. It has been shown that DEC-C causes redistribution of microfilariae in the body tissues (Duke *et al.*, 1976) and, more significantly, microfilarial destruction. Microfilarial death, whether spontaneous or as a result of DEC-C therapy, provokes inflammation in the cornea (Jones *et al.*, 1978), and a marked increase of inflammation is seen in the epidermis during DEC-C administration (Rougemont *et al.*, 1974). Inflammation appears to be an integral part of the therapeutic response to DEC-C therapy, and there is evidence to suggest that destruction of microfilariae is mediated by an immune response to surface antigens exposed by the action of DEC-C on the outer cuticle of the microfilaria (Rougemont *et al.*, 1974; Gibson *et al.*, 1976). It is unlikely that inflammation and optic nerve damage of the type reported here results from DEC-C alone, since they have not been described during animal toxicity studies (Harned *et al.*, 1948) or during mass population therapy in the absence of onchocerciasis (Kessel *et al.*, 1970; Che'en, 1964). It is generally agreed that the severe reactions during DEC-C treatment of onchocerciasis are related to destruction of microfilariae by the drug, and there is no evidence to suggest that microfilarial death induced by DEC-C is more likely to precipitate inflammation than spontaneous death, except in that the number of dying microfilariae after DEC-C is larger and therefore consequent response greater.

The pattern of disease seen in these patients receiving DEC-C resembled precisely the changes induced by onchocerciasis alone. The distribution of punctate retinal pigment epithelial lesions at the edge of the macula conformed with that seen before therapy and with that recorded in other parts of the world (Budden, 1973; Bird *et al.*, 1976). Similarly, the optic disc swelling with limitation of hyperfluorescence to the disc tissues, and the arcuate field loss also mirrored the untreated disease state. The only differences were the rapidity of onset and time course of the processes. It was as if DEC-C had compressed several years' disease into a few days, which would support the concept that the disorder in either circumstance was related to microfilarial death.

The difference between the optic nerve and choroidal pigment epithelial disease in response to DEC-C therapy was striking. Following a survey of Bussere villages (Zaroug *et al.*, in preparation) it was certainly our impression that the population from which our patients were drawn had a higher prevalence of optic nerve disease relative to choroidoretinitis (and sclerosing keratitis) than patients with onchocerciasis seen in other countries (Anderson and Fuglsang, 1977). It is possible that DEC-C therapy in communities elsewhere would provoke a different pattern of disease, and in particular that sustained choroidoretinitis might occur.

With such a short period of review the long-term effects of DEC-C treatment cannot be judged. It is possible that the functional deficit was temporary, but steroids, though given during a very short period, did not reverse the changes. Equally, it is possible that more patients may have suffered visual loss later than 8 days after starting DEC-C as a result of inflammation induced by treatment.

These observations, albeit on a small sample of patients from Southern Sudan without controls, have grave implications for DEC-C therapy in Sudan in particular and probably throughout the world and support the impressions gained as a result of previous studies (Anderson *et al.*, 1976a, Anderson and Fuglsang, 1978). The course of DEC-C given in this study is in accord with current therapeutic practice and appears to carry a high visual morbidity due to posterior segment disease, but this should be set against the possible benefit to the patient derived from suppression of anterior segment disease following DEC-C therapy (Anderson *et al.*, 1976a) and the visual loss which would occur in the untreated disease. Alternative therapeutic regimens, using long-term low-dose DEC-C, DEC-C combined with corticosteroids (Markell and Turner, 1957), or alternative microfilaricides, have been tried in the past in an attempt to avoid the

intense discomfort of high-dose DEC-C (Rougemont *et al.*, 1976). The apparent high risk to vision with DEC alone supports the rationale for seeking another way of controlling this disease, but any alternative therapeutic agent which causes massive microfilarial death may carry the same risk to vision in heavily infected patients unless it can be shown that changes detected in this study are somehow specific to DEC-C.

It is acknowledged that the action of suramin differs from that of DEC, and a similar study to that described here would be justified to assess its effect on the eye and the visual system. However, evidence exists to indicate that optic atrophy may follow treatment with suramin and that suramin therapy is also accompanied by severe systemic and ocular reactions (Anderson *et al.*, 1976b). Such a response may be due to the microfilaricidal action of suramin (Duke, 1968), and Anderson and Fuglsang (1978) have suggested that an acceptable therapeutic regimen may require an initial course of DEC-C combined with corticosteroids followed by injection of suramin. If such a complex regimen proves safe and effective, there would be considerable logistic difficulties in delivering this treatment to large populations.

All these problems might be resolved if a therapeutic agent which was only microfilaricidal existed which provided a means of eliminating adult worms from the body, allowing the microfilariae to die naturally during the ensuing 1–2 years. A single course of such a drug would be adequate in an area where there was *Simulium* control, but it would have to be repeated regularly where there was risk of reinfection. Clearly, patients heavily infected by *O. volvulus* present a major problem in management, and there is doubt whether the visual prognosis can be improved by any of the available therapeutic agents.

We thank Mr K. Sehmi for printing the photographs and Miss Julie Bramley for secretarial assistance. We are particularly grateful to Lieut. Col. Abuof for allowing us to use the facilities of the Military Hospital in Wau.

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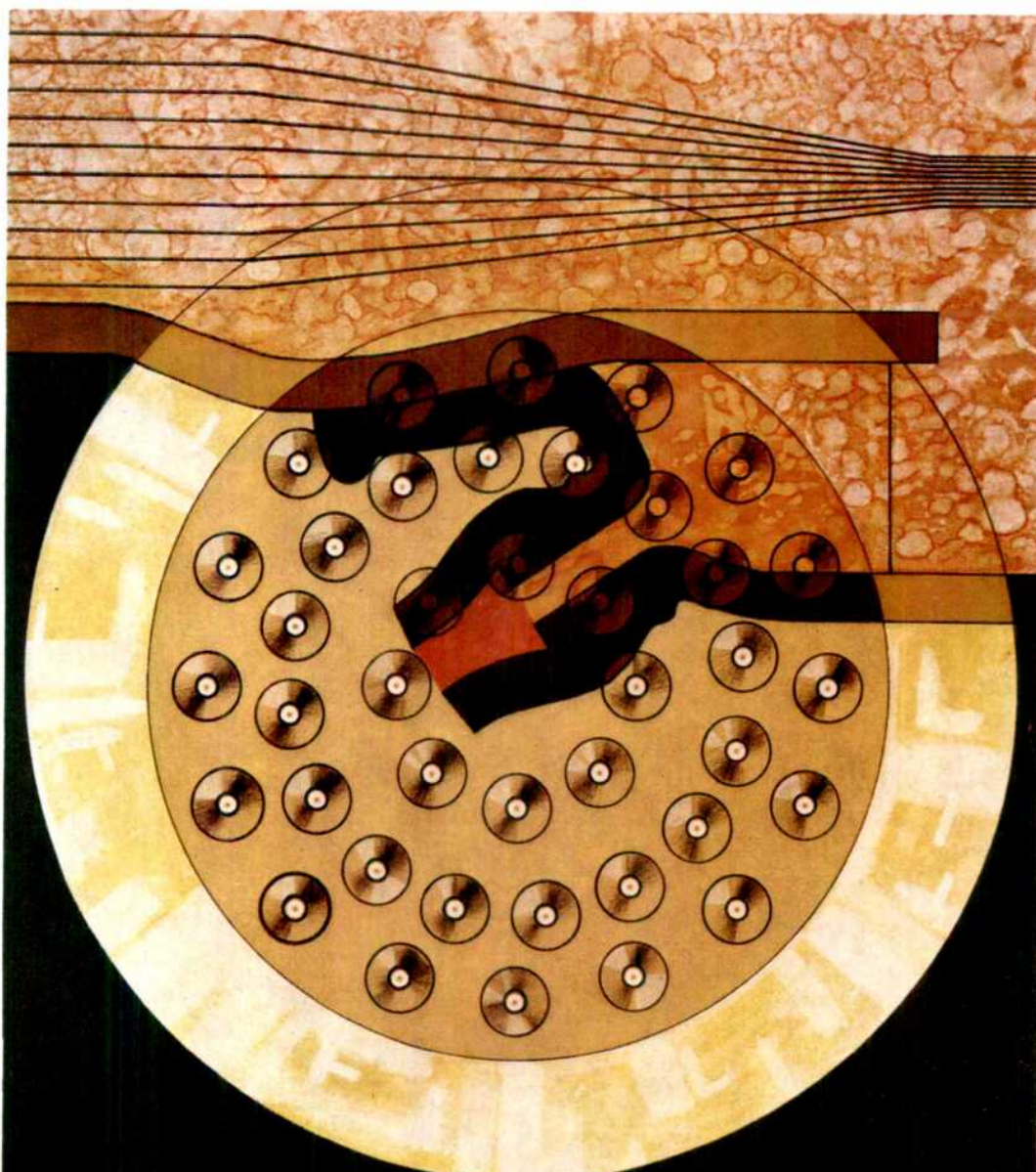
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Rubella maculopathy

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SUMMARY Three patients with known history of congenital rubella and sudden decrease of vision are presented. Two of the 3 patients had previous eye examinations which showed typical rubella (salt and pepper) retinopathy. All 3 showed macular lesions associated with presumed subretinal neovascularisation.

The ocular and systemic manifestations of congenital rubella were first recognised by Gregg in 1941.¹ His description included the triad of cataracts, congenital heart disease, and deafness of infants born in an Australian epidemic of rubella. However, no mention of fundus changes was made. Gregg attributed the first fundus observation to Mitchell,¹ who in 1939 described a child with left monocular cataract. Mitchell stated that the fundus of the patient's right eye appeared pale, and that some scattered irregular spots of pigment were observed. Previous authors have stressed that visual function remains stationary and that rubella retinopathy is a benign and nonprogressive condition.²⁻⁶ The purpose of this report is to demonstrate that this previous concept is not necessarily valid in all instances.

Case reports

CASE 1

The first case is that of an 11-year-old white male with a prenatal history of a maternal exposure to rubella during the first trimester. The length of pregnancy and delivery was normal. The patient had no significant systemic disease, but was diagnosed as having profound deafness at 5 weeks of age. There was no history of ocular trauma. The patient's previous ocular record shows that in 1975 the visual acuity was 20/20 in each eye. In February 1976 the vision in the right eye was corrected to 20/20 while the best correction in the left eye was 3/400. External examination was unremarkable except for some early bilateral band keratopathy. The anterior segment showed some scattering of

pigment on the anterior lens capsule in the left eye and a snowflake cataract in the right eye. Ophthalmoscopic examination of the right macula showed some pigment mottling with loss of the foveolar reflex (Fig. 1a).

In the left macula there was a yellowish fibrotic scar with a small punctate haemorrhage beneath the sensory retina (Fig. 1b). In the early laminar phase of the fluorescein angiogram diffuse and small pigment epithelial window defects in the macular region can be seen (Fig. 1c). Late phase of the angiogram shows increased hyperfluorescence due to the staining of the scar tissue, with some blockage of the background fluorescence by punctate haemorrhage beneath the sensory retina (Fig. 1d).

CASE 2

The second case is that of an 11-year-old black male with a prenatal history of maternal rubella during the first trimester of pregnancy. At 18 days of age the child was admitted to hospital for surgical repair of a patent ductus arteriosus and at that time was found to have a severe hearing defect. In March 1976 the patient complained of decreased vision in the left eye. There was no history of ocular trauma. Vision in the right eye was 20/20, while vision in the left eye was correctable to only 20/400. Anterior segments of both eyes were normal.

Ophthalmoscopic examination of the left posterior pole showed diffuse pigment epithelial mottling with a salt and pepper appearance. In the macular region there was a yellowish fibrotic scar (Fig. 2a). The fluorescein angiogram of the left posterior pole showed both hyperfluorescence and blocked fluorescence due to the diffuse pigment epithelial mottling. There was an increased hyperfluorescence directly within the foveolar region due to staining of the disciform scar (Fig. 2b).

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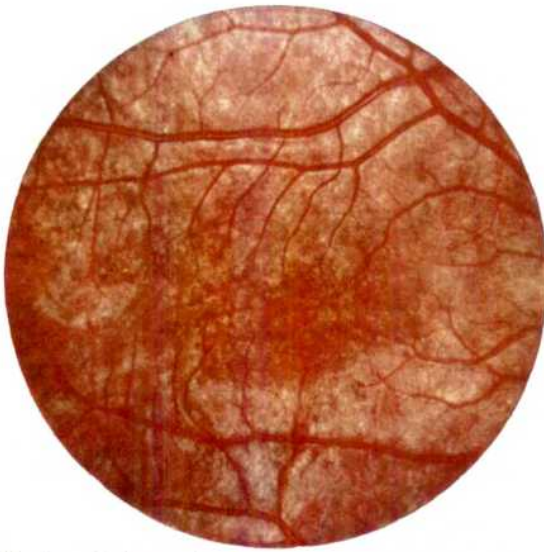


Fig. 1a Right macula: pigment mottling with loss of the foveolar reflex.

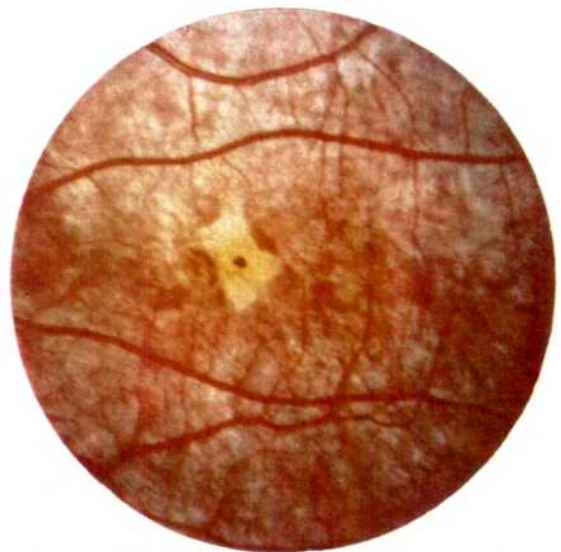


Fig. 1b Left macula: a yellowish fibrotic scar with a small punctate haemorrhage beneath the sensory retina.

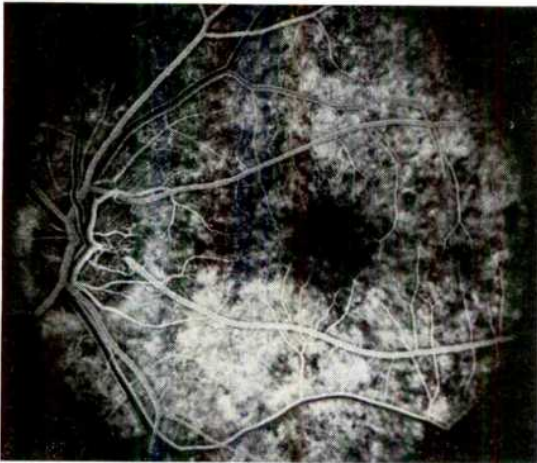


Fig. 1c Early laminar phase of the fluorescein angiogram reveals diffuse small pigment epithelial window defect. There is increased blockage in the macular region secondary to the fibrotic tissue.

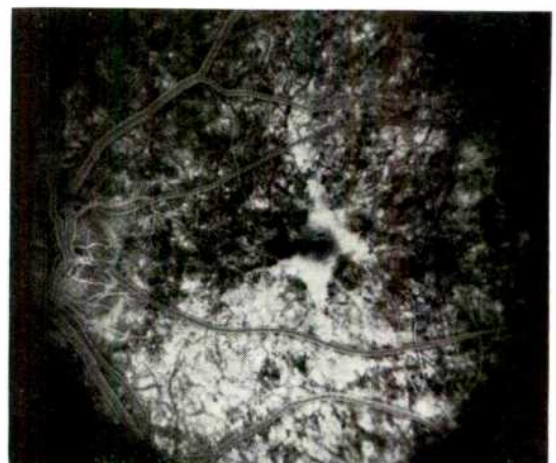


Fig. 1d Late phase of the fluorescein angiogram shows increased hyperfluorescence due to staining of the scar tissue with blockage of the background fluorescence by the punctate subretinal haemorrhage.

CASE 3

Case 3 is that of a 12-year-old white male with a prenatal history of maternal exposure to rubella virus during the first trimester of pregnancy. The patient was found to be deaf at 4 months of age. In 1976 the best corrected visual acuity was reported as 20/30 in the right eye and 20/20 in the left eye.

In November 1977 the patient's best corrected visual acuity in the right eye was found to be 20/400,

while vision in the left eye was 20/20. There was no history of ocular trauma. The external examination as well as the anterior segment examination were within normal limits.

The midperiphery of the right eye showed a typical salt and pepper pigmentary mottling (Fig. 3a). The left macula showed generalised mottling of the pigment epithelium with loss of both the macular ring and foveolar reflexes² (Fig. 3b).



Fig. 2a Left macular region; diffuse pigment epithelial mottling with a salt and pepper appearance and a yellowish fibrotic disciform scar.



Fig. 2b Venous phase of the fluorescein angiogram reveals both hypo- and hyperfluorescence due to the pigment epithelial mottling. Increased hyperfluorescence is seen within the foveolar region due to staining of the disciform scar.

In the right posterior pole there was a small serous detachment of the sensory retina with a small subretinal haemorrhage. A greyish discoloration could be seen inferior to the haemorrhage (Fig. 3c).

Early in the laminar phase of the angiogram

there was an increased blockage of fluorescence in the macula due to subsensory retinal and subretinal pigment epithelial haemorrhage (Fig. 3d). In the venous phase of the angiogram there was still blockage of the background fluorescence. Also seen was an area of increased hyperfluorescence due

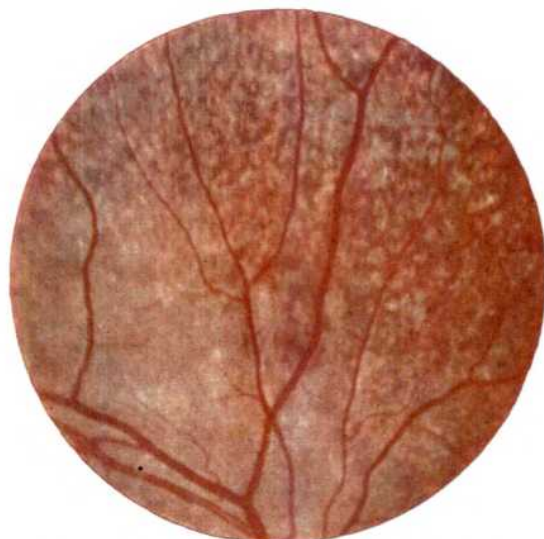


Fig. 3a Midperiphery of the right eye; a typical salt and pepper pigmentary mottling.

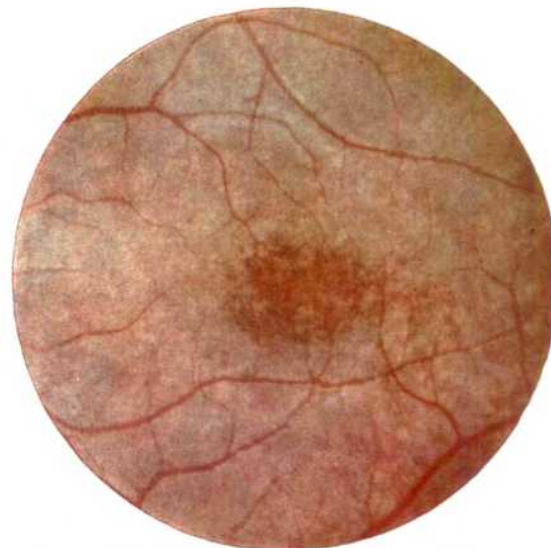


Fig. 3b Left macula; generalised mottling of the pigment epithelium with loss of both the macular ring and foveolar reflexes.

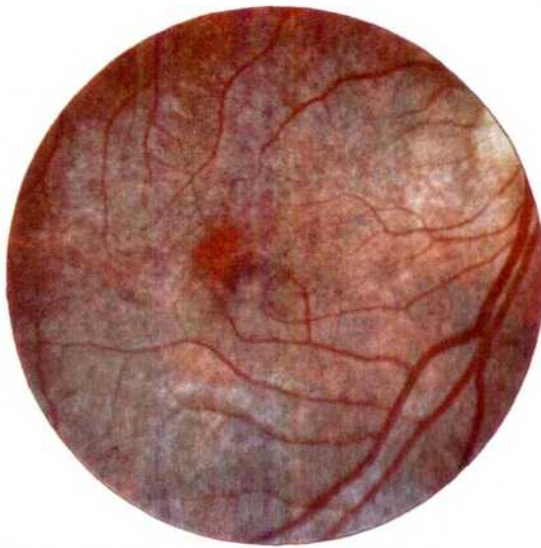


Fig. 3c Right macular region: a small serous detachment of the sensory retina with subretinal haemorrhage. A greyish discoloration can be seen inferior to the haemorrhage.

to fluorescein leakage, presumably from subretinal neovascularisation (Fig. 3e).

Discussion

These 3 cases of rubella maculopathy, in addition to the 3 recently reported by Deutman and Grizzard,⁸ point out that disciform formation secondary to subretinal neovascularisation is a definite complication which can develop in patients with rubella retinopathy. Rubella maculopathy must now be added to the ever expanding list of disorders associated with subretinal or subretinal pigment epithelial neovascularisation. At present we have no histopathological evidence that these disciform scars in patients with rubella maculopathy are due to the persistence of the rubella virus. The authors feel that the pre-existing disease at the level of the retinal pigment epithelium and Bruch's membrane is most likely the cause for the development of subretinal neovascularisation and the eventual disciform scar.

In conclusion, we have studied 3 cases of congenital rubella retinopathy with macular lesions, associated with presumed subretinal neovascularisation. Although a typical subretinal neovascular membrane was not seen in our cases or the case reports presented by Deutman and Grizzard, the presence of fibrotic macular scars and subretinal haemorrhage are highly suspicious of previously existing subretinal neovascularisation. It is important not to

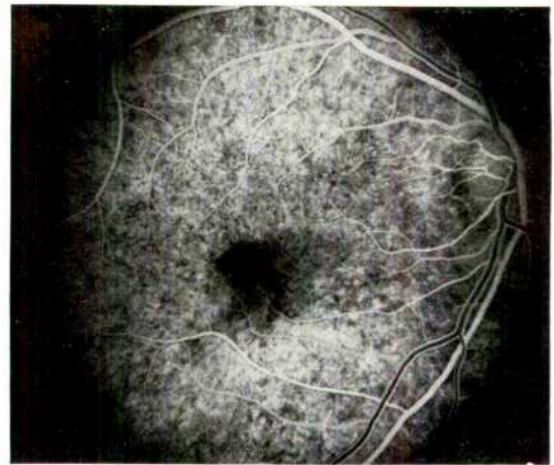


Fig. 3d The laminar phase of the angiogram shows increased blockage of fluorescence in the macula due to subsensory retina and subretinal pigment epithelial haemorrhage.

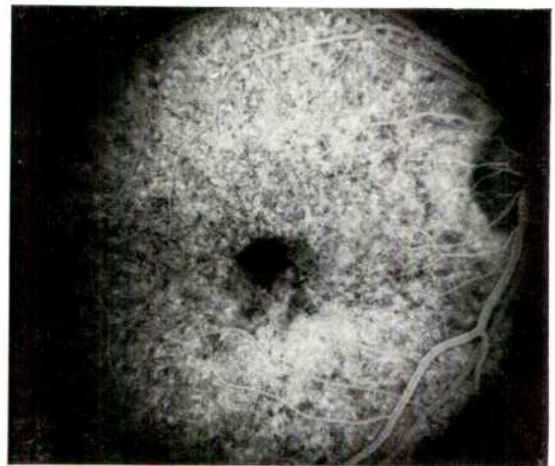


Fig. 3e Venous phase of the angiogram continues to show blockage of the background fluorescence. There is an area of increased hyperfluorescence due to fluorescein leakage presumably from a subretinal neovascular membrane.

attribute automatically a decrease of visual acuity in rubella patients to cataracts or amblyopia. It is necessary to look diligently for a macular lesion. Subretinal neovascularisation and macular haemorrhage result in fibrotic macular scars, which lead to a significant reduction in central acuity.

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Infantile cystoid maculopathy

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SUMMARY Three premature infants with no family history of eye disease showed bilateral cystoid maculopathy on post-mortem examination. These macular lesions are indistinguishable macroscopically from the macular lesions of sex-linked juvenile retinoschisis. Cystoid change was observed at various vertical retinal levels. The oldest child had a schisis cavity within the nerve fibre layer. All cases had reduced numbers of retinal ganglion cells and central nervous system (CNS) abnormalities. The authors believe these are the first reported cases of a cystoid macular lesion present at birth and the first description of the pathological features of a cystoid macular lesion in infants.

Cystoid macular change in infants is often a manifestation of hereditary eye disease.¹ With a hereditary cause in mind it has been postulated that these macular lesions exist at birth, yet such an observation has not been reported.² At necropsy we have observed cystoid maculopathy in 3 premature infants without a history of familial eye disease. Similar macular changes have been noted clinically since at least 1898,³ yet the histopathological features of this lesion in children have never been described. This paper presents these histopathological features and reports the existence of such a cystoid maculopathy at birth.

Materials and methods

The material for this study included both eyes from 3 infants examined at necropsy either at the UCLA Center for the Health Sciences or at the Los Angeles County Harbor General Hospital over a 15-year period. All eyes were taken within 2 to 6 hours of death.

Preparation, gross sectioning, macroexamination, and recording of findings were performed according to our routine methods.⁴ Microsections were prepared from celloidin-embedded eyes stained with haematoxylin-eosin and peroxidic acid Schiff technique and alcian blue to determine the location and contents of these spaces.

Case reports

CASE 1

A black infant boy weighing 820 g was born to a healthy 24-year-old woman. The pregnancy was unremarkable. Fetal heart tones were present on admission to hospital for delivery. Three generations of family members were contacted by telephone and letter, and no history of eye disease was found. Father and brother were examined and their eyes were found to be normal. Delivery was complicated by premature rupture of membranes. The child survived 11 days before succumbing to respiratory distress syndrome. Supplemental oxygen therapy was necessary to maintain a PO_2 of between 21 and 177 mmHg.

Significant systemic necropsy findings were restricted to immaturity of the white matter of the central nervous system.

Ocular examination. The right eye measured 14.2 mm (AP) $\times$ 14.8 mm (H) $\times$ 13.5 mm (V). The left eye measured 14.1 mm (AP) $\times$ 14.5 mm (H) $\times$ 13.6 mm (V). When incised, both eyes showed cystoid changes in the maculae (Fig. 1). The peripheral retina and vitreous cavity were unremarkable. On light-microscopical examination notable findings included bilateral cystoid change confined to the macula and involving predominantly the outer nuclear layers. These cavities were outlined by Müller cell pillars. The retinal ganglion cells were markedly reduced in number. The peripheral retina was unremarkable (Fig. 2).

CASE 2

This was a stillborn infant girl weighing 1.45 kg

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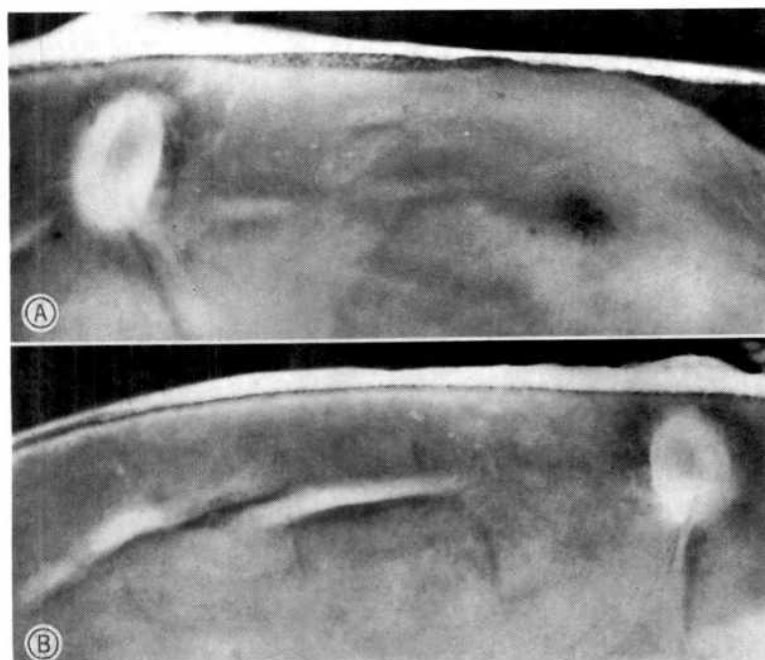


Fig. 1 Case 1. Macroscopic appearance of macular lesions. (A) Right eye showing multiple small cystoid change, radially arranged ($\times 18$). (B) Left eye showing a more subtle similar lesion than (A) ($\times 18$).

born to a healthy 29-year-old Hispanic woman. There was no family history of eye disease. The delivery was complicated by placental abruption.

Post-mortem examination revealed an anencephalic infant with a cervical meningocele, who was otherwise appropriately developed for her birth weight.

Ocular examination. The right eye measured 16.2 mm (AP) $\times$ 16.8 mm (H) $\times$ 16.6 mm (V);

the left eye 16.4 mm (AP) 16.8 mm (H) $\times$ 16.6 mm (V). The 2 eyes were unremarkable with the exception of cystoid lesions in the maculae. The peripheral retina and vitreous cavity were unremarkable. Except for the macular lesions both eyes were unremarkable on microscopic examination. In the macula were moderately reduced numbers of ganglion cells and cystoid spaces that involved the inner nuclear layer. The Müller pillars were stretched

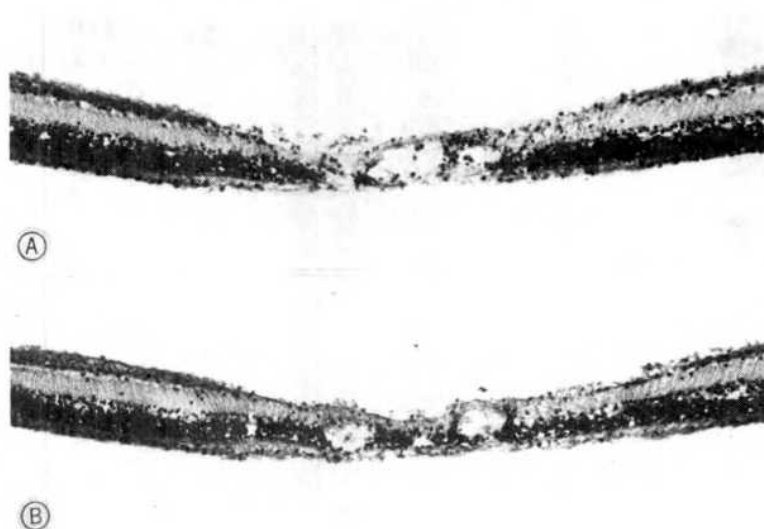
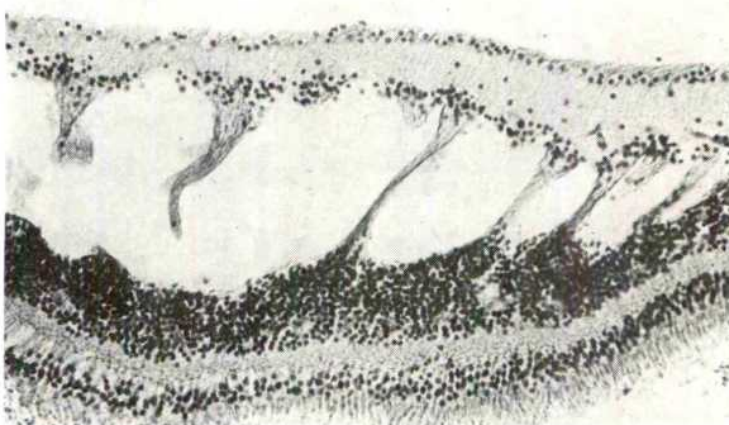


Fig. 2 Case 1. Microscopic appearance of macular lesions. (A) Right eye showing multiple cystoid spaces involving the outer nuclear layer (haematoxylin-eosin, $\times 142$). (B) Left eye showing less extensive cystoid maculopathy (haematoxylin-eosin, $\times 142$).

Fig. 3 Case 2. Macula showing extensive cystoid change in middle retinal layers with stretched and seemingly broken Müller pillars on left. Note similarity to typical cystoid degeneration of peripheral retina (haematoxylin-eosin, $\times 146$).



across these cavities (Fig. 3). The peripheral retina was unremarkable.

CASE 3

A white stillborn boy weighing 3.32 kg was born to a healthy 25-year-old woman. There was no family history of eye disease. Fetal heart sounds were present when the mother arrived at the hospital for delivery. The pregnancy and delivery were uncomplicated.

The necropsy showed hydrocephalus, spina bifida, and patent ductus arteriosus. The infant was otherwise normal for his birth weight.

Ocular examination. Both eyes were large. The right measured 21.2 mm (AP) $\times$ 19.0 mm (H) $\times$ 19.9 mm (V); the left eye, 21.1 mm (AP) $\times$ 20.0 mm (H) $\times$ 18.8 mm (V). Both corneas measured 9.8 mm (H) $\times$ 11 mm (V). When incised both eyes showed large excavation of the optic nerve head. Central cystoid lesions and paracentral schisis cavities were observed within the macula in each

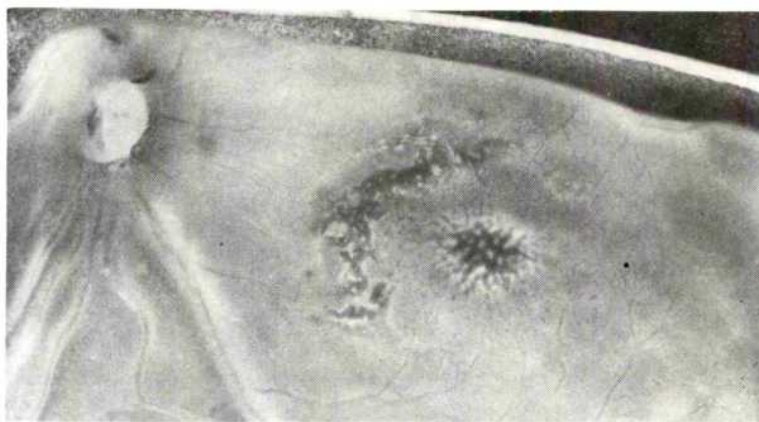
eye (Fig. 4). The peripheral retina and vitreous cavity were unremarkable.

Both macular lesions in each eye were examined microscopically. The more central lesion showed cystoid change within the nerve fibre layer. A small amount of haemorrhage was contained in one of these spaces (Fig. 5A). The paracentral lesion was a large schisis cavity within the nerve fibre layer, which had lost the radial support of the Müller pillars (Fig. 5B). The number of ganglion cells was moderately reduced. The anterior chamber angles were dysplastic. The peripheral retina and vitreous were unremarkable.

Discussion

These 3 cases show cystoid changes in the maculae of both eyes. Cavitation was present at various retinal levels and in the oldest infant large schisis cavities were within the nerve fibre layer. Macroscopically these lesions are identical to the macular

Fig. 4 Case 3. Macula of left eye showing central cystoid change with Müller pillars intact (white dots) and paracentral crescent-shaped area of macular schisis with loss of Müller pillars ($\times 17$).



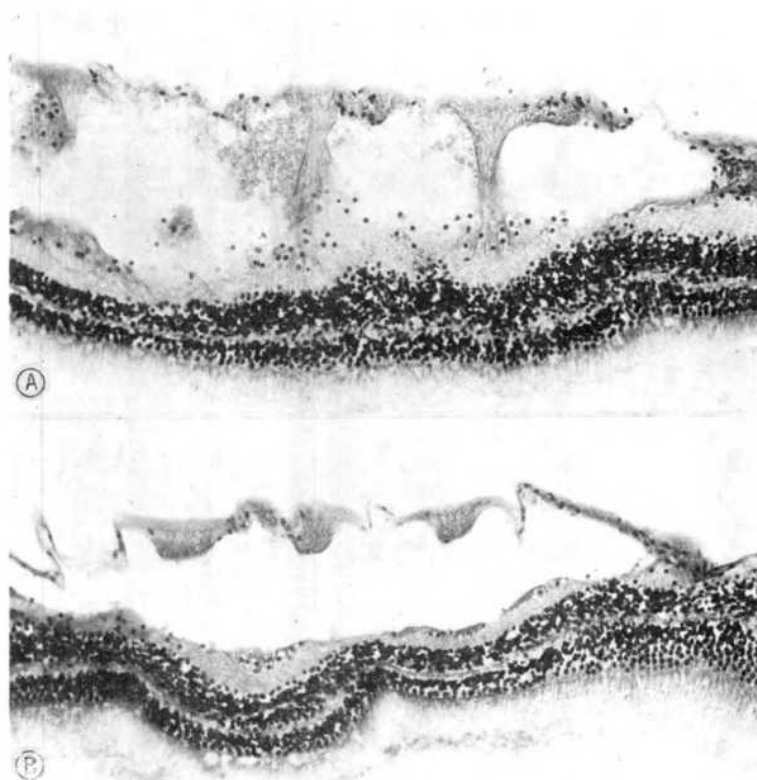


Fig. 5 Case 3. Macula of left eye. (A) Central lesion showing cystoid change within the nerve fibre layer and Müller pillars stretched across cavities. Note similarity to peripheral reticular cystoid degeneration (haematoxylin-eosin, $\times 114$). (B) Paracentral lesion showing loss of Müller pillars and formation of a large reticular-like (bullous) schisis cavity within the nerve fibre layer (haematoxylin-eosin, $\times 160$).

lesions of sex-X-linked retinoschisis, but in view of the negative family history of eye diseases this diagnosis is unlikely. Since 50% of patients with sex-X-linked retinoschisis have only macular lesions, however, the possibility of a spontaneous genetic mutation must be considered.⁵ Some authors consider that cystic macular change precedes peripheral retinoschisis.⁶

Yanoff *et al.*⁷ postulated that the underlying defect in sex-X-linked retinoschisis is in the inner cytoplasm of Müller cells, which allows retinoschisis cavities to form. In our cases the Müller cells are stretched and broken across cystoid/schisis cavities, adding support to the hypothesis of Yanoff *et al.* As in hereditary juvenile retinoschisis the retinal cavities in our cases contained no acid-mucopolysaccharide material. In all cases the peripheral retina was unremarkable.

It is well known that the peripheral retinoschisis lesions of sex-X-linked retinoschisis tend to affect the nerve fibre layer and cause large bullous thin-walled cavities extending into the vitreous.⁷⁻¹⁰ The macula of an affected child has never been described. Manschot¹¹ has described the eyes of a 60-year-old man who was a member of a family known to have the gene for X-linked retinoschisis, and these eyes showed wrinkling of the internal limiting

lamina and splitting of the nerve fibre layer with normal underlying retinal tissue. Our eyes showed reduced ganglion cells seemingly related to the patients' concomitant CNS changes.

Von Sallman¹² pointed out that generalised retinal cystoid changes and even splitting of the nerve fibre layer can be produced by prepartum compromise of the carotid jugular circulation in rhesus monkeys. These lesions, although extensive, did not involve the macula. In our cases there is no evidence, from the general necropsy data or from the ocular pathological findings to support an ischaemic aetiology for the selective macular lesions seen in these 3 infants. In all cases retinal ganglion cells were reduced in number. All children had central nervous system abnormalities, which may relate to the poorly developed ganglion cell layer. One case had a patent ductus arteriosus seemingly unrelated to the ocular changes. The authors have been unable to determine if these retinal and CNS lesions are meaningfully associated or if the CNS lesions only allow the fortuitous necropsy study of these eyes.

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Macular changes resulting from papilloedema

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SUMMARY Six cases are presented with macular changes in association with papilloedema: 4 suffered permanent visual loss. The present paper emphasises this previously infrequent finding and discusses the haemodynamic and mechanical factors responsible. The macular changes consisted of haemorrhages situated in front, within, or behind the retina, and occasionally the results of neovascular membrane formation produced secondary visual loss. Changes in the pigment epithelium were seen in 3 cases associated with choroidal folds. Macular stars rarely produce visual loss. Recognition of these changes is important in the assessment of the visual loss in papilloedema.

Visual loss as a result of papilloedema is usually due to atrophy and degeneration of optic nerve fibres and macular involvement as a cause has been neglected. This neglect is reflected in the paucity of well documented reports and the absence of any correlation with visual loss.

Schmidt and Wegener¹ described speckling of the macula in 2 patients with papilloedema due to intracranial tumours. Paton² in a review of patients with papilloedema at the National Hospital mentions that small white dots seen in a parabolic shape occurred in 5 cases. Similar observations were made by Colrat,³ and both authors emphasised the absence of visual deterioration. One report of a macular hole and papilloedema⁴ may represent only a chance finding.

The aetiology of cystic changes at the macula in post-mortem cases of disc oedema was discussed by Samuels,⁵ though he failed to differentiate papilloedema from local causes of disc oedema. The absence of recent reports suggests that ophthalmologists should be consulted when visual deterioration is a feature of papilloedema.

This paper presents 6 selected cases of macular changes occurring in the presence of papilloedema (the term papilloedema being restricted to cases of disc oedema due to raised intracranial pressure) studied at the National Hospital by fluorescein angiography.

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Case reports

CASE 1

A 56-year-old woman was admitted to the National Hospital under the care of Dr Gooddy on 18 April 1973 with a long history of headaches of increasing severity over the last year and associated with gradual visual loss.

On examination she had a mild right spastic hemiplegia with bilateral extensor plantar responses.

Investigations included a plain skull x-ray, left carotid arteriogram, right vertebral arteriogram, ventriculogram, air encephalogram, and Myodil ventriculogram. These showed severe symmetrical hydrocephalus, without evidence of a tumour and a ventriculo-atrial shunt was inserted.

Ocular examination. Visual acuity was 6/24 in the right eye and counting fingers in the left eye with a large central scotoma. There was bilateral papilloedema with narrowing and sheathing of vessels and multiple small infarcts surrounding the discs. A massive preretinal haemorrhage was visible at the left macula (Fig. 1a), and then gradually absorbed with a resultant improvement in vision (Fig. 1b).

Conclusion. Temporary visual loss due to a preretinal macular haemorrhage occurred in a patient with bilateral chronic papilloedema.

CASE 2

This 55-year-old woman was admitted to the Brook General Hospital on 13 May 1970 under the care of

Dr Hierons with a 3-month history of frequent obscurations.

At that time the only finding was bilateral papilloedema. Skull x-rays, EEG, gamma scan, and examination of the cerebrospinal fluid were normal. A ventriculogram showed no enlargement of the ventricles, and a provisional diagnosis of benign intracranial hypertension was made.

In October 1970 the visual acuity in the left eye suddenly deteriorated and perimetry showed a

central scotoma. On 9 March 1971 she was admitted to the National Hospital under the care of Professor Gilliatt, and a lumboperitoneal shunt was inserted by Professor Logue. This had to be revised in 1972. After this procedure her symptoms have improved with resolution of the obscurations, and the disappearance of papilloedema.

Ocular examination. Her visual acuity was 6/5 in the right eye and 6/60 in the left eye. There was bilateral enlargement of the blind spots and a left central scotoma. The fundi showed bilateral papilloedema with an extensive subretinal haemorrhage in the left eye which encircled the optic disc to involve the macula, together with a large subpigment epithelial haemorrhage supero-temporal to the disc which produced displacement of the retinal vessels.

Fluorescein studies showed (Figs. 2a and b) dilatation of the peripapillary plexus, tortuosity of the retinal vessels superotemporally, and traction on the macula. Choroidal fluorescence was visible above, but obscured below by the large subretinal haemorrhage. Repeat studies 9 months later showed restriction of the leakage to the vascular membrane.

Conclusion. Permanent visual loss resulted from a choroidal and subretinal haemorrhage in the macular region in a patient with benign intracranial hypertension.

CASE 3

A 53-year-old Hungarian was admitted to the National Hospital under the care of Dr Blau on 9 March 1972 with a history of severe episodic headaches for many years associated with a recent deterioration of vision. On admission he had an occipital bruit but no other neurological signs. Carotid and vertebral angiography revealed a large occipital dural arteriovenous malformation.

In April 1972 after a subarachnoid haemorrhage the feeding vessels to the malformation were ligated.

Ocular examination. Visual acuity was 6/18 in each eye, and visual fields showed large blind spots with a relative central scotoma in each eye. Fundus examination showed there was bilateral papilloedema with linear choroidal folds encircling the disc and radiating across the macular area. The choroidal folds persisted after treatment, and fluorescein angiography demonstrated their distortion of the macular area. Leakage of dye into the retina was visible in relation to a linear fold immediately above the macula in the left eye (Fig. 3) and similar distortion though with less leakage was visible in the right eye.

Conclusion. Bilateral visual loss resulted from macular distortion and choroidal folds in a patient with raised intracranial pressure due to an occipital dural arteriovenous malformation.

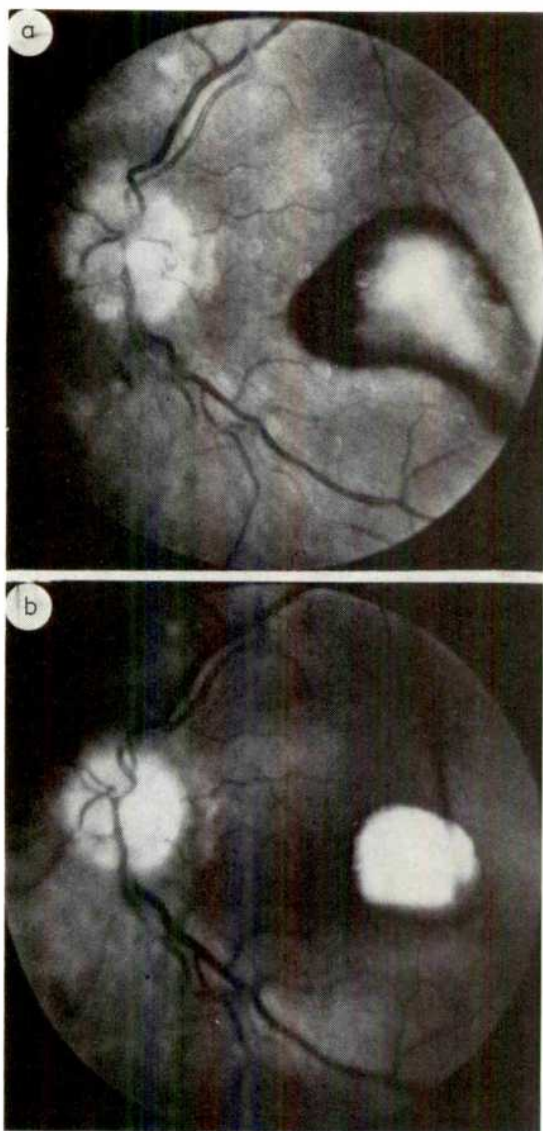


Fig. 1 Case 1: (a) Copy of colour photograph showing a large preretinal haemorrhage at the macula, (b) which 5 weeks later had largely resolved.

CASE 4

A 26-year-old man was first admitted to the National Hospital on 3 November 1971 under the care of Dr Denis Williams with a history of unsteadiness on his feet for 4 months, nausea, occipital headaches, and an inability to look to the right. He had obscurations of vision for 1 month before admission.

On admission he had a left cerebellar ataxia, left

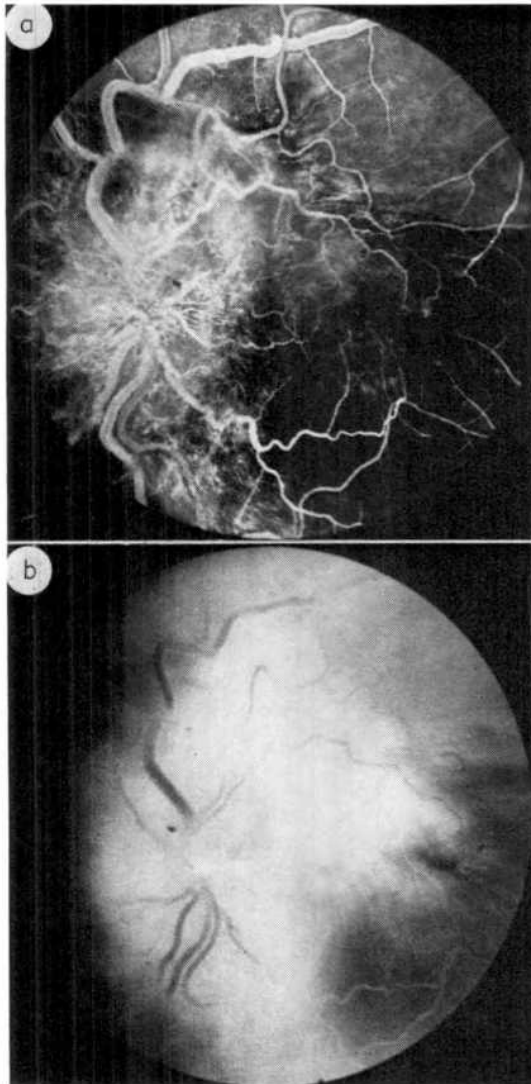


Fig. 2 Case 2: (a) Fluorescein angiogram in the venous phase showing dilatation of the peripapillary capillaries with vesicular distortion due to macula traction. The choroidal fluorescence is obscured below by an extensive subretinal haemorrhage. (b) Residual picture taken at 10 minutes to show extensive leakage at the optic disc extending superotemporally towards the macula.



Fig. 3 Case 4: Fluorescein angiograms showing the choroidal folds extending through the macula with hyperfluorescence occurring over one of the folds. Right eye in a venous phase.

sided weakness, and a right VIth nerve palsy. A posterior fossa tumour was diagnosed by vertebral angiography and ventriculography.

On 6 November 1971 a cystic cerebellar astrocytoma was removed from the left cerebellum. Post-operatively he made a good recovery.

Ocular examination. At admission his visual acuity was 6/18 in the right eye and 6/36 in the left eye, with a left temporal field loss and a right paracentral loss. Examination of the fundi showed gross papilloedema with dilatation of the superficial papillary and peripapillary plexuses. The peripapillary retina was swollen, with a well defined macular star and numerous haemorrhages and microaneurysms.

Fluorescein study showed an abnormally dilated superficial capillary plexus extending into the retina above and below the disc. This appeared to fill from the retinal system. Numerous microaneurysms were present on the disc surface, and there was gross leakage of dye from both discs in the late stages.

Visual acuity improved to 6/6 and 6/36 post-operatively.

Conclusion. Bilateral macular stars were associated with papilloedema due to a cerebellar astrocytoma. Visual reduction in the left eye was attributed to amblyopia.

CASE 5

A 54-year-old woman with symptomless papilloedema was referred by Dr Mackenzie for fluores-

cein angiography. No other neurological abnormality was found, and investigations which were normal included skull x-ray, brain scan, EEG, carotid angiogram, and a ventriculogram. In view of these findings a diagnosis of benign intracranial hypertension was made, and after a course of steroid therapy resolution of her papilloedema occurred.

Ocular examination. The visual acuity in each eye

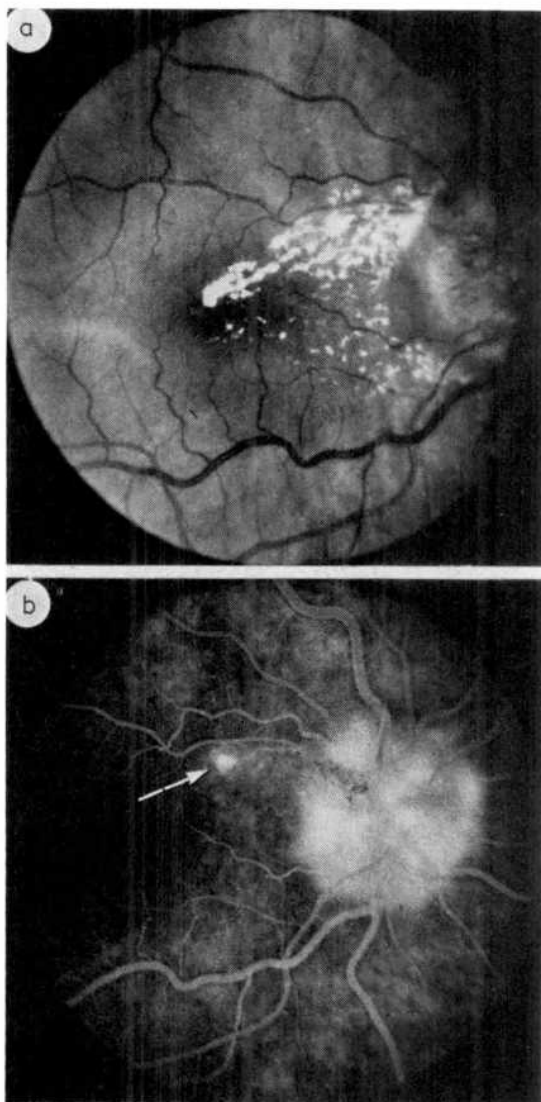


Fig. 4 Case 5: Copy of a colour photograph of the right eye showing a macular star, and fluorescein angiography. (b) Showed leakage of dye at the disc with a smaller area of focal leakage superotemporal to the disc.

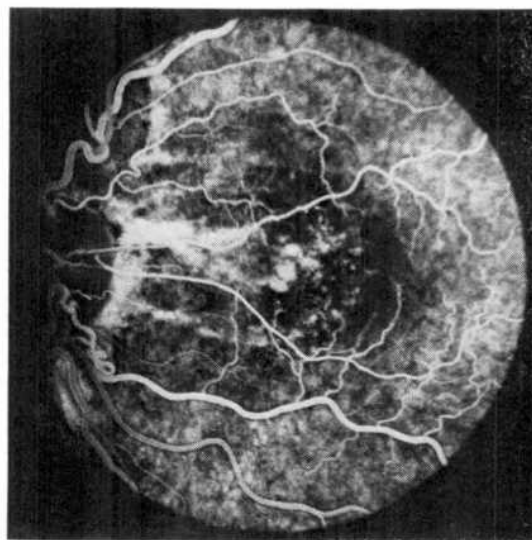


Fig. 5 Case 6: Fluorescein angiogram in the late phase shows linear transmission defects extending from the disc to the macula with diffuse nodular areas of hyperfluorescence at the macula.

was 6/24 and perimetric examination showed enlarged blind spots. There was bilateral chronic papilloedema and in the right eye multiple lipid exudates condensed to form a macular star (Fig. 4a).

Fluorescein angiography showed dilatation of the papillary plexus with extravasation of dye. In the right eye there was an area of focal leakage superotemporal to the disc (Fig. 4b, arrow).

Conclusion. A macular star with reduced visual acuity occurred in a patient with bilateral papilloedema due to benign intracranial hypertension.

CASE 6

A 6-year-old boy was admitted to the National Hospital in 1944 with otitic hydrocephalus. His cerebrospinal fluid pressure was 300 mmHg, and massive macular stars were described in both eyes by Mr Williamson Noble.

Ocular examination in 1971. His visual acuity was 6/9 in the right eye and 6/36 in the left eye, and his visual fields had central scotomata together with moderate enlargement of his blind spots. The optic discs were pale, the retinal vessels showed tortuosity at the disc margin, and pigment epithelial defects were visible at both maculae.

Fluorescein angiography showed attenuation of the arteries with linear pigment epithelial defects around the disc. In the macular regions punctate and nodular areas of hyperfluorescence were visible (Fig. 5).

Conclusion. Visual loss resulted from pigment

epithelial changes at both maculae in a patient with otitic hydrocephalus.

Discussion

PATHOPHYSIOLOGY OF PAPILLOEDEMA

Raised intracranial pressure produces papilloedema if the intracranial and perioptic nerve sheaths are in communication. Incision of the optic nerve sheath in experimental animals⁶ and in man⁷⁻¹¹ produces resolution of disc oedema. Elevation of the CSF pressure in the optic nerve subarachnoid sheath produces both haemodynamic and mechanical changes at the optic disc and peripapillary region. The haemodynamic changes include delayed choroidal filling of the optic disc and peripapillary region, with compensatory dilatation of the retinal papillary and peripapillary plexus. Fluorescein angiography demonstrates the delayed choroidal filling, and the early filling of retinal peripapillary capillaries suggests that the vessels are functioning as compensatory shunt vessels.¹² The raised pressure in the optic nerve sheaths transforms this structure into a rigid tube, which indents the posterior globe, producing acquired hypermetropia and choroidal folds.¹³

The extension of both the haemodynamic and mechanical effects to the macular area when the papilloedema is either severe or long standing is therefore not surprising, and the cases selected for this report indicate the varieties of macular involvement.

HAEMODYNAMIC EFFECTS

Haemorrhages. Haemorrhages in the nerve fibre layer are a constant feature of fully developed papilloedema. Situated normally in relation to the optic disc, they may become preretinal or spread into the vitreous.² Their occurrence at the macula is rare, but is facilitated by marked dilatation of the radial peripapillary plexus, by impaired function of the endothelial cells as in the elderly, and when ocular perfusion is labile. The prognosis for vision is good, as resolution usually ensues.

Peripapillary haemorrhages in the subretinal layer are often seen in papilloedema, but ophthalmoscopic recognition is difficult owing to obscuration by the overlying disc tissue. They presumably represent abnormal permeability of the choroidal capillaries. Haemorrhages deep to the pigment epithelium (case 2) produce a major destruction of the retina with scarring and gliosis resulting in retinal distortion and traction. The prognosis for vision is poor but this manifestation is fortunately rare.

Macular star. The constellation of hard exudates

that represents a macular star is more frequently seen in accelerated hypertension with disc oedema than in papilloedema. Gross papilloedema with massive fluorescein leakage at the optic disc is usually seen without macular exudates. The pathophysiological requirements for the development of a macular star are not known, but the following factors are probably contributory: (1) impaired retinal and choroidal perfusion to an area with high metabolic needs; (2) increased capillary permeability with leakage of large molecular weight lipoproteins.

The disc fluorescence rarely extends to the macular region even in the most severe cases, and macular fluorescence is not a concomitant finding in star formation. One patient (case 5), however, showed a focal area of leakage from a retinal vessel which may have been contributory.

MECHANICAL FACTORS

Distension of the distal optic nerve sheaths with CSF under high pressure may indent the posterior globe, with resultant hypermetropia, and permanent pigment epithelial changes due to folding or wrinkling of the choroid which was first described by Nettleship.¹⁴ The mechanism was discussed by Bird and Sanders,¹⁵ who described 2 main types: (1) the broad folding of the choroid with hyperfluorescent crests and troughs which show reduced fluorescence; (2) pigment epithelial wrinkling.

COMBINATION OF HAEMODYNAMIC AND MECHANICAL FACTORS

The combination of impaired peripapillary choroidal perfusion and the indentation by the distended nerve sheath may produce severe degenerative and hypoxic changes in the peripapillary choroid (case 6). The macula may therefore be involved at a preretinal, retinal, or pigment epithelial level.

We thank the consultants of the National Hospital for referring these patients to the Neuro-ophthalmology Unit, Miss Gaye Hopkins for secretarial assistance, and Mr Rolf Sennhenn for the photography.

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Identification of T and B lymphocytes in the human conjunctiva and lacrimal gland in ocular diseases*

RUBENS BELFORT JR. AND NELSON F. MENDES

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SUMMARY The presence and localisation of T and B lymphocytes in biopsy specimens of human conjunctiva and lacrimal gland from 34 patients were studied in frozen sections. Eighteen patients had follicular conjunctivitis, 13 patients had Sjögren's syndrome, and 3 were normal. All cases of follicular conjunctivitis showed a similar picture. B cells were in higher number than T cells, but both types of lymphocytes were present in the infiltrates. In the developed follicles T cells occupied the periphery and B cells the central part of the infiltrates. In patients with Sjögren's syndrome the conjunctival biopsies showed a higher number of B lymphocytes. The number of T cells was higher in the lesions from Sjögren's syndrome than in cases of follicular conjunctivitis. The infiltrate in lacrimal gland biopsies showed T cells which were scattered while B cells were more numerous and formed clusters close to vessels. Normal conjunctiva and lacrimal gland showed no adherence of either sheep erythrocytes or human erythrocytes sensitised with antibody and complement.

Recent advances in immunology now permit the distinction between human thymus-dependent (T) and thymus-independent (B) lymphocytes based on different membrane receptors (see Mendes, 1977).

Human T cells bear receptors for sheep erythrocytes (E) and human B cells bear receptors for C3b. These receptors enable the identification of T and B cells in suspension or in tissue sections by rosette formation or by adherence of the corresponding indicator. Human erythrocytes sensitised with antibody and complement (HEAC) or zymosan-C3 complexes (ZC) have been used as indicators of B cells (Mendes *et al.*, 1974b; Kajdacsy-Balla and Mendes, 1976).

We have applied these methods to identify T and B cells in inflammatory infiltrates in biopsies obtained from patients with follicular conjunctivitis of different aetiologies and Sjögren's syndrome in order to verify the nature of the infiltrates in several eye diseases. Since certain nonlymphoid tissues may bear C3b receptors as found in renal glomeruli (Gelfand *et al.*, 1975), we also looked for these receptors in normal ocular conjunctiva and lacrimal gland.

*Presented at the Third International Symposium on Ocular Immunology and Immunopathology, San Francisco, 1978.

Correspondence to Dr Belfort.

Patients and methods

PATIENTS

We studied 31 patients with the following diagnoses: 18 with follicular conjunctivitis (comprising 9 caused by adenovirus, 3 by chlamydia, 1 by herpes simplex, 1 by molluscum contagiosum, 1 secondary to the use of 5-iodo-2'-deoxyuridine (IDU), 1 with chronic microbial allergic conjunctivitis, and 2 with chronic folliculosis, and 13 patients with Sjögren's syndrome.

All patients with follicular conjunctivitis were submitted to conjunctival biopsy. In the group with Sjögren's syndrome a conjunctival biopsy was performed in 11 and a lacrimal biopsy in 4 patients. Three normal volunteers were also submitted to conjunctival and lacrimal gland biopsy.

IDENTIFICATION OF T AND B LYMPHOCYTES IN TISSUE SECTIONS

We have used the method described in detail by one of us elsewhere (Silveira *et al.*, 1972; Mendes *et al.*, 1974a, b).

Our current technique uses 6 µm thick cryostat sections which are dried at room temperature for 10 minutes and then covered with one drop of either 0.5% E suspension in Hanks's balanced salt solution or 0.5% HEAC in phosphate buffered

saline pH 7.2, containing EDTA (1.7×10^{-3} M). The sections were incubated at 37°C for 15 minutes and then for 1 hour at 4°C in a moist chamber. The excess indicator was removed by placing the sections over saline (0.15 M sodium chloride) at 4°C for 20 minutes, thereby allowing the nonadherent erythrocytes to settle by gravity. The slides were then dried, fixed with absolute methanol, and stained with haematoxylin-eosin.

The degree of adherence of the markers to the lymphocyte infiltrate was classified from 0 to ***.

Results

Follicular conjunctivitis. The results in Table 1 show that, independently of the aetiology, the follicles were constituted predominantly by B cells as detected by the adherence of HEAC. In well developed follicles T lymphocytes as detected by the adherence of E showed a peripheral disposition, while B cells occupied the central area (Figs. 1 and 2).

Sjögren's syndrome. The conjunctival biopsies showed a higher number of B cells. T lymphocytes were present, and their number was higher than in cases of follicular conjunctivitis (Table 2). The lacrimal gland biopsies also revealed a greater proportion of B cells forming large clusters, while T cells were scattered. A large number of lymphocytes did not show adhesion either to HEAC or to E.

Discussion

For the first time the methods used to identify T and B cells have been applied to the study of the nature

of the mononuclear cell infiltrate in the conjunctiva and lacrimal gland in several diseases.

Our findings have shown that different aetiologies of follicular conjunctivitis lead to the same kind of infiltrates, which are constituted mainly of B cells, with T cells present in the periphery of the follicle.

Previous studies on salivary gland biopsies have shown that B cells constitute the major population

Table 1 Degree of adherence of E and HEAC in conjunctival biopsies from patients with follicular conjunctivitis

Diagnosis	Degree of adherence	
	E	HEAC
Adenovirus	*	**
	**	***
	*	***
	*	***
	*	**
	*	**
	*	**
	*	***
Chlamydia	*	***
	0	***
	*	*
Chronic folliculosis	*	**
	**	***
IDU	0	*
Molluscum contagiosum	**	**
Herpes simplex	*	***
Chronic microbial allergic	*	**

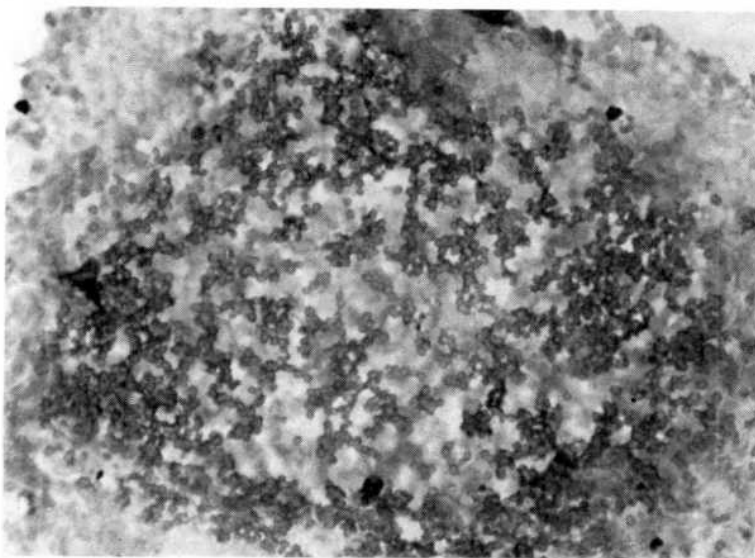


Fig. 1 Follicular conjunctivitis: adherence of HEAC to B lymphocytes (haematoxylin and eosin) $\times 100$

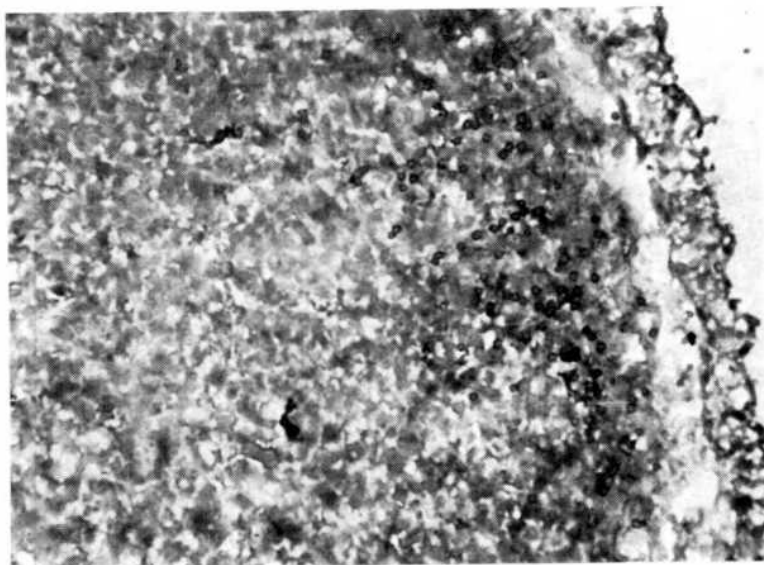


Fig. 2 Follicular conjunctivitis: adherence of E to T lymphocytes (haematoxylin and eosin) $\times 100$

Table 2 Degree of adherence of E and HEAC in conjunctival and lacrimal gland biopsies from patients with Sjögren's syndrome

E	HEAC
<i>Conjunctival biopsy</i>	
*	**
*	***
**	**
**	***
*	**
*	*
*	*
<i>Lacrimal gland biopsy</i>	
*	***
**	***
**	**
**	***

of lymphocytes in lesions from patients with Sjögren's syndrome (Scheinberg *et al.*, 1976). Our results have also revealed a greater number of B cells in conjunctival and lacrimal gland infiltrates in this syndrome.

The normal conjunctival and lacrimal gland biopsies which were examined by the same method

revealed no adherence of either E or HEAC, indicating that nonlymphoid cells in these tissues do not bear receptors for E or for complement.

Supported by FAPESP, CNPq, CAPES, and FINEP.

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Pigmentation associated histopathological variations in sympathetic ophthalmia

GEORGE E. MARAK, JR., AND HIROSHI IKUI

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SUMMARY The severity of inflammation in sympathetic ophthalmia is related to the degree of pigmentation, and the granulomatous response seems to be related to pigmentation. Eosinophilia is also associated with pigmentation, but this association appears to be fortuitous and is a result of the association of eosinophilia with severity of the inflammation.

Elsching presented his most confusing pearl to the ophthalmological community when he proposed that sympathetic ophthalmia represented an autoimmune response to uveal pigment.^{1,2} Recent observations have raised considerable doubts about the role of uveal pigment as the offending antigen in sympathetic ophthalmia.^{3,4} The function of the uveal melanocytes in sympathetic ophthalmia is not well understood, but pigmentary disturbances occur clinically, and some histopathological features of sympathetic ophthalmia appear to be associated with uveal pigmentation.⁵ The purpose of this report is to evaluate the previously described association of certain histopathological features of sympathetic ophthalmia with pigmentation in a new population.

Materials and methods

Cases were selected for this study from the files on sympathetic ophthalmia at Kyushu University, Fukuoka, Japan, and from the Armed Forces Institute of Pathology (AFIP), USA, that fulfilled well established clinical and histopathological criteria for the diagnosis of sympathetic ophthalmia outlined by Easom and Zimmerman.⁶

In the present study 2 groups of patients were selected who appeared to be intermediate in pigmentation between the black and white groups of patients described in a previous report.⁵ One group of patients were Japanese and the second group was a heterogeneous collection of Indian subcontinent, American Indian, Puerto Rican, Middle East, and non-Japanese oriental patients who might

reasonably be considered intermediate in pigmentation between North American black and white populations.

The magnitude of choroidal thickening by the inflammatory infiltrate, the intensity of tissue eosinophilia, and the proportion of the epithelioid cell response in the choroid compared to the lymphocytic infiltration were rated by a single observer who was 1 of the 3 independent observers among whom there was essential agreement in all cases in the prior study.⁵

The choroidal inflammatory reaction was rated mild if the greatest thickness of the postequatorial choroid did not exceed half of a 'high-dry' field (430 $\times$), moderate if the choroidal thickness exceeded one-half but was less than 1 complete high-dry field, and marked if the thickness of the postequatorial choroidal inflammation exceeded 1 full high-dry field.

The epithelioid cell response was evaluated by comparing the relative proportion of choroidal thickening accounted for by the nests of epithelioid cells compared to the lymphocytic infiltrate. Eosinophils were considered to be increased if 3 or more were seen in the choroid in 5 representative high-dry fields. This increase was considered heavy if more than 20 eosinophils were seen in a high-power field.

Results

The 2 groups of cases of sympathetic ophthalmia were chosen because they appeared to represent degrees of pigmentation intermediate between the white and black patients. The histopathological features of sympathetic ophthalmia that seem to be associated with pigment were observed to occupy

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an intermediate position with respect to the severity of the inflammation, the epithelioid response, and the degree of eosinophilia (Table 1). Although increased eosinophilia is associated with increased pigmentation (Table 2), this association may be fortuitous and simply reflect the observation that eosinophilia is a function of the severity of disease in all groups studied (Table 3). The epithelioid response appeared to be more closely related pigmentation. In severe cases in whites the epithelioid response is not as predominant as in black patients, though the degree of epithelioid response is difficult to quantitate.

Discussion

Our observations confirm the previously described association between degree of pigmentation and the intensity of uveal inflammation in sympathetic

ophthalmia. As predicted, patients with pigmentation intermediate between black and white patients have a form of sympathetic ophthalmia showing intermediate intensities of inflammatory reaction.

Fuchs originally suggested that the pigment containing epithelioid cells in sympathetic ophthalmia may represent modified uveal melanocytes.⁷ This possibility has been discussed in some detail by Hogan and Zimmerman, who point out⁸ that there is insufficient tissue necrosis in sympathetic ophthalmia to account for the amount of apparent pigment 'phagocytosis'.

Current evidence suggests an alternative to the belief that the pigment-containing epithelioid cells have phagocytosed the alleged offending uveal pigment. The hypothesis that pigment-containing epithelioid cells represent modified uveal melanocytes is supported by several studies. Various intermediate stages between melanocytes and the so-called pigment-containing epithelioid cells have been observed.⁹⁻¹⁰ Autophagy of melanosomes by pigment-containing cells has been described.¹¹ There has been a detailed demonstration that the epithelioid cells of Dalen-Fuchs nodules are modified retinal pigment epithelial cells.¹²⁻¹³

A recent observation on the association of an experimental form of sympathetic ophthalmia with inflammation of the pineal gland suggests that a disturbance in melatonin metabolism may provide a link between the uveal inflammation and pigmentary disturbances.¹⁴

The association of eosinophilia with pigmentation appears to be fortuitous, as there are no known mechanisms of association. This appears to be a reflection of the correlation between eosinophilia and the severity of the inflammation. The association of eosinophilia with severe inflammation and the relative concentration of eosinophils in the inner choroid have important immunological implications. In experimental sympathetic ophthalmia eosinophils occur only in the more severe forms of disease, are associated an increase in antibodies to the sympathogenic antigen, and may be suppressed by the C3 inactivator factor of cobra venom (which depletes complement and interferes with immune complex disease). These observations suggest that an immune complex mechanism of pathogenesis may participate in very severe forms of disease, though the basic pathogenic mechanism appears to involve cell mediated hypersensitivity.¹⁵

The preferential localisation of eosinophils in the inner choroid in both human and experimental sympathetic ophthalmia may be a reflection of the site at which the immunological surveillance system first encounters the sympathogenic antigen, which is presumably released from the immunologically

Table 1 *Degree of inflammatory thickening of the choroid in sympathetic ophthalmia*

Pigmentation	No. of patients	Choroidal thickening (per cent)		
		Mild	moderate	Severe
Caucasians	218	60	24	16
Mixed group	19	21	37	42
Japanese	25	24	28	48
Black	34	11	29	60

Table 2 *Eosinophilia in the choroid of sympathetic ophthalmia*

Pigmentation	No. of patients	Percentage with Eosinophilia
Negro	34	39
Mixed group	19	23
Japanese	25	24
Caucasians	218	9

Table 3 *Eosinophilia as a function of inflammation*

Eosinophilia*	Mild (%)	Moderate (%)	Severe (%)
Negroes (13)	15	15	70
Japanese (7)	0	43	57
Mixed (5)	20	20	60
Caucasian (19)	10	15	75

*Three or more eosinophils in the choroid in 5 representative high-dry fields.

privileged site between the middle limiting membrane of the retina and Bruch's membrane as a result of the digestion of outer segment containing phagosomes by the retinal pigment epithelium.^{3,4}

Our understanding of the pathogenesis of the pigment-containing epithelioid cells in sympathetic ophthalmia is uncertain. Recent evidence suggests that the hypothesis that the pigment-containing epithelioid cells in sympathetic ophthalmia represent modified uveal melanocytes may be considered as an alternative to the opinion that these cells have phagocytosed the pigment. These alternatives can be tested when reliable specific surface markers are developed for macrophages and melanocytes.

The authors are indebted to Professor L. E. Zimmerman for his thoughtful advice.

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Book reviews

A Colour Atlas of Endocrinology. By R. HALL, D. EVERED, and R. GREENE. Pp. 175. £18.00. Wolfe Medical Publications: London. 1979.

As the authors state in their introduction, endocrinology is a specialty with a large and variable visual content. Those aspects that are largely visual have been lavishly illustrated by numerous high-quality colour illustrations, and those topics that have a small visual content have been dealt with in a diagrammatic or tabular form. The result is a useful atlas that, while not in any way pretending to be comprehensive, covers most aspects of the subject in a way that is interesting and easy to read. The illustrations are all pertinent to the content of the book, even though there is a little duplication. Although ophthalmologists may not be excited by the standard of the eye photographs, it would be unlikely that they would be looking in this book for enlightenment about the eye signs in these conditions. But any ophthalmologist would certainly benefit from glancing through its pages to refresh his memory of classical aspects of endocrinology and to bring himself up to date on those aspects with which he is not fully conversant. Altogether this is a useful book that can be recommended for ophthalmologists at all stages.

DAVID TAYLOR

The Eye. Vol. 1. By R. C. AUGUSTEYN, H. B. COLLIN, and K. M. ROGERS. Pp. 177. £14.00. Churchill Livingstone: Edinburgh. 1979.

This volume reviews work published on the biochemistry and physiology of ocular tissues (other than the retina) between July 1976 and June 1977 and covers some 550 papers. It is divided into 13 chapters, each dealing with a particular tissue, and the text consists chiefly of what are in fact short abstracts of the various individual papers. So far as the present reviewer can judge, these are adequate and can serve as a source of further reading, though they are for the most part uncritical, and the user of this volume must regard them as such. The authors have obviously undertaken a very difficult task, in which it is hoped they will persist, but the cost in the United Kingdom seems rather high considering that some of the papers mentioned were published more than 3 years ago.

DAVID COLE

Correspondence

Living larya of *Onchocerca volvulus*

TO THE EDITOR, *British Journal of Ophthalmology*

SIR, I am sending you a photograph of a living larva (microfilaria) of *Onchocerca volvulus*, seen in Ghana in 1953 during field surveys. I used a slit-lamp adapted to give a magnification of $\times 45$. This gave an excellent view—despite the difficulties encountered by eye move-

ments—of the passage of this larva under the corneal epithelium and above Bowman's membrane. It struggled along slowly, with resting periods, apparently with some



difficulty, but it did make progress. The magnification of the photograph is $\times 4340$.

F. C. RODGER

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Notes

Low vision

The First Australian/Pacific Conference on Low Vision, sponsored by the Australian National Council for the Blind, will be held in Melbourne on 19–21 May 1980. The theme is 'Low vision ahead'. Further details from Mr Lindsay McMillan, Conference Organiser, Association for the Blind, HM Lightfoot Centre, 454 Glenferrie Road, Kooyong, Victoria, Australia.

Vitrectomy course

The University Eye Clinic of Lausanne, Switzerland, will sponsor a 2-day vitrectomy course on 26–27 October 1980. The programme will cover basic and advanced concepts of pars plana vitrectomy in proliferative retinopathies, traction retinal detachments, retinal detachments with massive preretinal proliferation, giant tears, intraocular foreign body, posterior segment perforation, and panophthalmitis. Registration fees: SFr300. Further information from Dr M. Gonvers, Clinique ophtalmique universitaire, 1004 Lausanne, Switzerland.

Israel international symposium

An international symposium will be held under the auspices of the Israel Ophthalmological Society at the Tel Aviv Hilton on 3–5 September 1980. The main topics will include congenital glaucoma; surgical and medical treatment; value of provocative tests in open-

angle and narrow-angle glaucoma; narrow-angle and angle-closure glaucoma; a definition, diagnosis, surgical versus medical treatment; ocular hypertension; breakthrough in medical treatment of glaucoma; selection of surgery in open and narrow-angle glaucoma; laser iridectomy; use of visual fields; value of diurnal curve. Further information from the Secretariat, POB 16271, Tel Aviv, Israel.

Obituary

Petrus Johannes Waardenburg, MD

Dr P. J. Waardenburg, of Arnhem, Holland, the ophthalmic geneticist renowned for his description of Waardenburg's syndrome, died on 23 September 1979 aged 93.



He was born in 1886 and studied medicine at the Rijksuniversiteit in Utrecht from 1904 to 1911. He then followed specialisation in ophthalmology under Professor Snellen Jr, of Utrecht, who promoted him to receive the MD in 1913 for his thesis on research in human inheritance of various physiological and pathological characteristics of the eye. In the same year he married and also studied under Professor Fuchs at Vienna. At the end of that year he settled in the Dutch country town of Arnhem as an ophthalmologist, continuing to practise there until 1952.

For the years 1934–40 he was external university lecturer in medical genetics at the Rijksuniversiteit in Utrecht. In 1931–5 he was secretary of the Netherlands Ophthalmological Society and in 1949–63 president of the Netherlands Anthropogenetic Society, of which he was a founder member. He was made honorary member of these 2 societies as well as of similar Danish, Italian, and German societies. In 1954 he was made honorary doctor of the Rijksuniversiteit in Leiden and of the Wilhelms Universität of Münster in 1964. In 1957 he received the Royal decoration Order of the Dutch Lion

and in 1959 the Snellen medal. In 1965 he founded the Waardenburg prize for special merit in the medical-genetic field. Between 1961 and 1974 the 3 volumes of his book *Genetics and Ophthalmology* were published. Until 1970 he gave genetic advice in paternity cases in the Dutch legal courts and genetic counselling.

Dr Waardenburg was a talented painter and musician, and these skills are reflected in the cultural abilities of his family. He is survived by his wife, 1 medical son and 4 daughters (of these 1 pair of identical twin daughters were obviously a great joy to his inquiring mind and enabled him to conduct twin studies on the spot).

Between 1910 and 1970 he published 267 papers in all. They included original observations on albinism¹ and many other hereditary conditions. He contributed the chapter on heredity in eye disease to *Modern Trends in Ophthalmology*.

Waardenburg's syndrome, or more fully, the van der Hoeve-Halbertsma-Waardenburg-Klein syndrome, was first described in its characteristic feature of outward displacement of the inner canthi causing blepharophimosis,^{2–4} but Waardenburg was the first to correlate this with congenital deafness and pigmentary defects of the iris and head hair.⁵

What amazed everyone so much about his research work and publications was that he did nearly everything unaided. The fieldwork, correspondence, most of the typing and drawing he did himself; only later in his life did the occasional secretary and pedigree artist give some help. He would not acknowledge anything he had not verified himself and was strict and accurate about all he did and wrote. Even in his last years there was a yearning to understand more.

His friends and colleagues all admired his immense knowledge and also his readiness to help fellow doctors and students. His kindness and modesty were a particularly endearing aspect of him. When I last saw him he was still trying to complete research studies even at the age of 89. He secured for himself a permanent place in the history of ophthalmology with his original work in ophthalmic genetics and his magnificent textbooks on the subject.

K. F. WILLIAMSON

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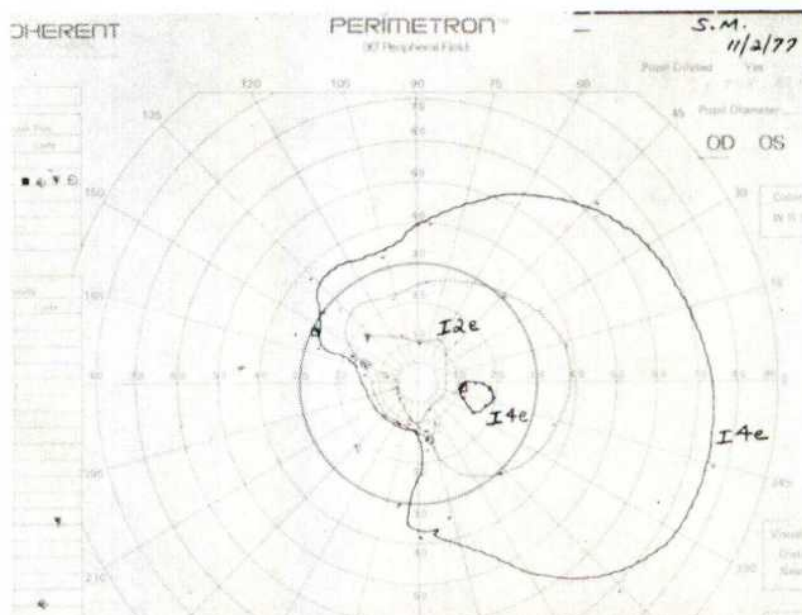
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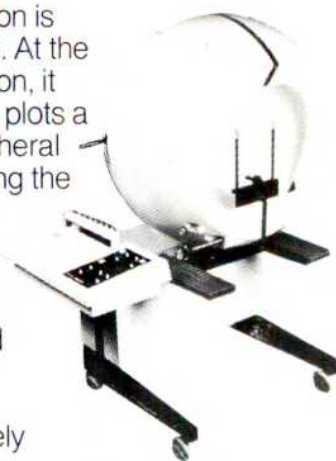
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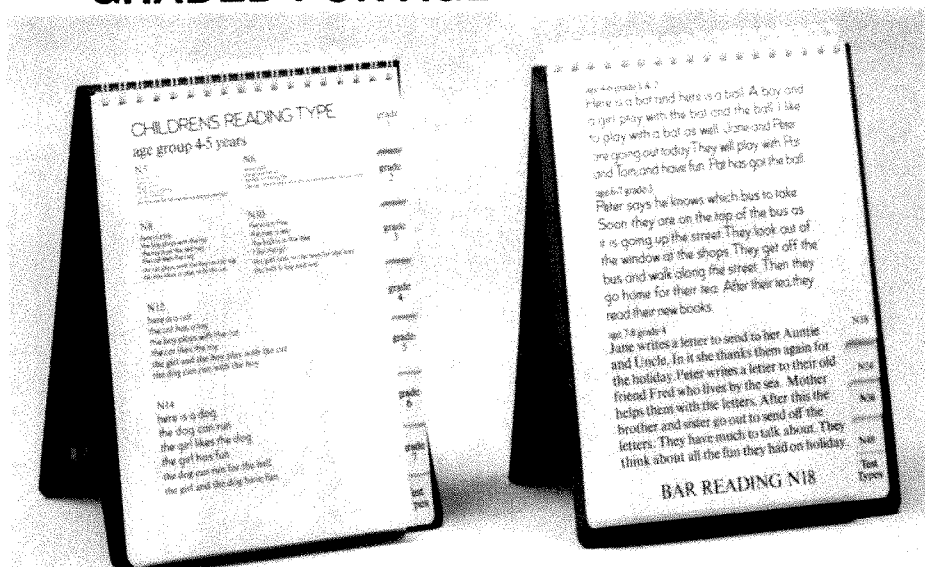


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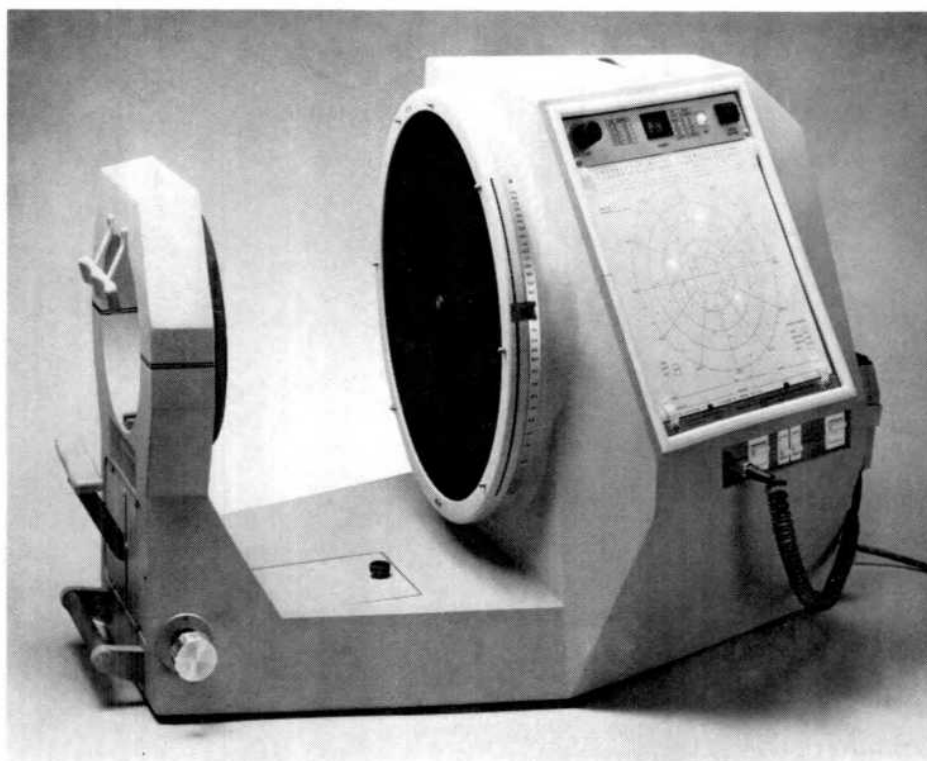
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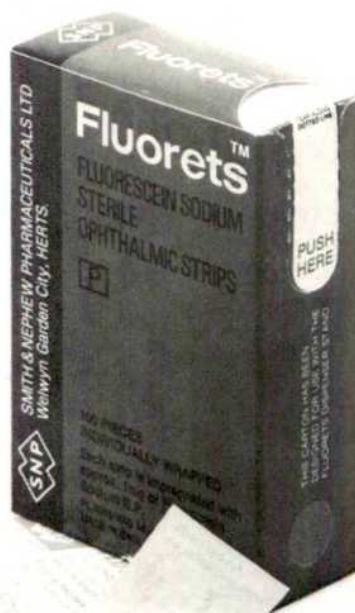
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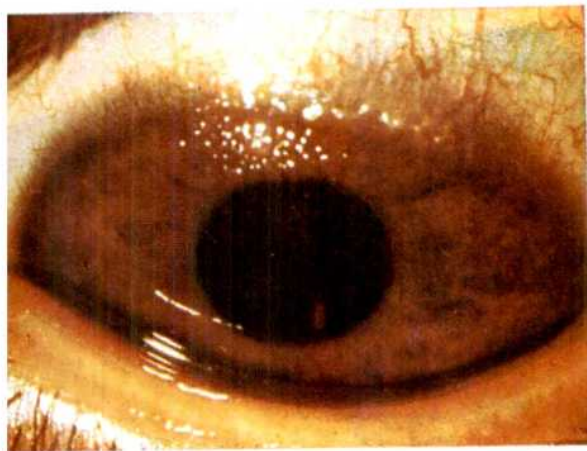
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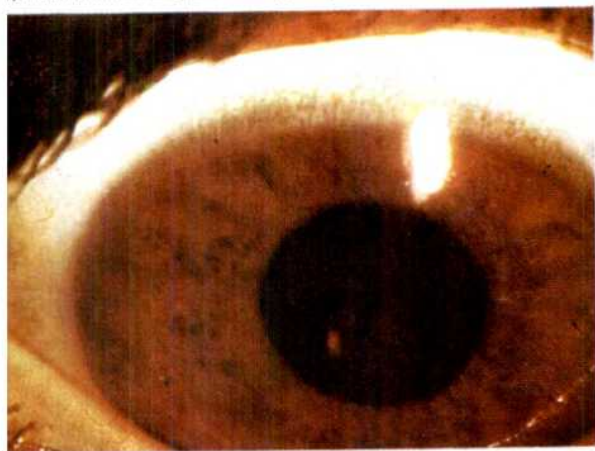
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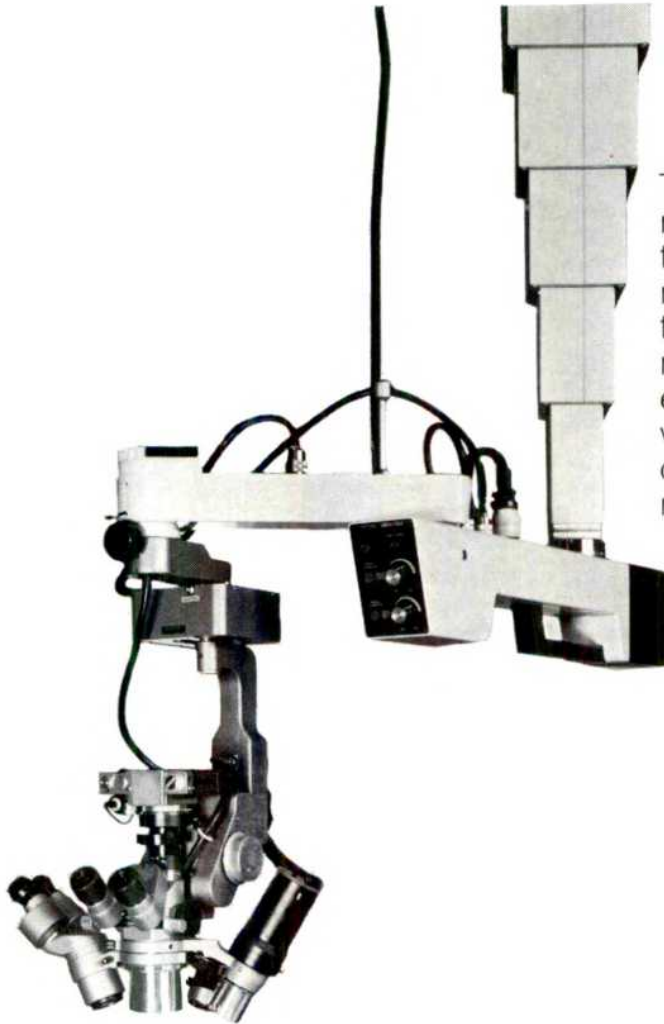
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Editorial: Genetic associations of glaucoma

Haemophilia and retinitis pigmentosa each result from the presence, in homozygous or heterozygous form, of a single specific pathogenic gene. A second gene may be linked on the same chromosome with a pathogenic gene, and the manifestation of this second gene—for example, a particular blood group—will accompany the disease in any one family. But because of crossing over of genes in sexual reproduction different alleles will be linked with the pathogenic gene in other families, so that the disease in question will not invariably be associated with the manifestation of the same gene (in this example the same blood group). In the population as a whole there will be no statistical association between the disease and the manifestation of any one allele.

There are many diseases which are common in particular families but which cannot be explained by classical Mendelian patterns. This is because the inheritance of them is polygenic. A number of genes must be present to overstep the threshold needed for the development of the full-blown disease.

Miller¹ has emphasised that in the 2 main forms of primary glaucoma each has a familial incidence, and almost invariably only one type occurs in a particular family. Both appear to be polygenic in inheritance, but in each case—in some families at least—one gene has a preponderant effect. A pharmacogenetic system which influences the incidence of chronic simple glaucoma expresses itself primarily in variations in response of intraocular pressure to topically applied dexamethasone. In closed-angle glaucoma the depth of the anterior chamber has a marked effect. This hereditary anatomical feature is mainly determined by one genetic system. Alsirk² has shown that in Greenland Eskimos there is a high incidence of shallow anterior chambers, and closed-angle glaucoma is relatively common. There are sufficient clues, however, in the pedigrees of patients with glaucoma to indicate that other genes are involved apart from the one principally responsible, and it is a fruitful pursuit to try to identify them.

Apart from specific pathogenic genes most of the recognisable genes in man concern blood groups (and factors). If such a gene is involved in the aetiology of a disease, there should be a statistical association in the population as a whole between the blood group and the disease. Blood groups vary in frequency between different populations. Part of this variation is the result of random processes

(genetic drift), but much, and perhaps most of it, is due to natural selection related to the differing environments, physical and microbiological, in which the populations live.

The world distribution of a number of other genetically determined characters has been studied. An example is the hereditary presence (or absence), in the saliva of the individual's ABO blood group antigen, which is referred to as ABH secretion (or nonsecretion). Another is the ability (or inability) to taste certain thyroid-inhibiting derivatives of thiourea, such as phenylthiocarbamide. Individuals are usually called PTC tasters (or nontasters). Some of these genetically determined characters are associated with specific diseases. However, it is important to realise that in order to establish the statistical association of a disease with other genetically determined characters large numbers of observations must be made. When the disease is uncommon this involves combining data, by established statistical methods, from a number of different research centres.

The statistical associations of glaucoma have attracted attention because it has been claimed that this disease (usually of unspecified type) tends to be associated with goitre (again mostly of unspecified type), and 2 of the firmly attested associations of disease with genetic polymorphisms concern goitre and PTC tasting. Sufferers from nontoxic goitre include an excess of nontasters, and sufferers from toxic goitre an excess of tasters.^{3,4}

Several searches have been made for associations between PTC tasting and glaucoma. The overall results⁵ show a raised incidence of nontasters among patients with primary chronic simple glaucoma and of tasters among patients with closed-angle glaucoma. A small number of cases of congenital glaucoma show a large excess of tasters. Moreover Becker *et al.*⁶ found low levels of protein-bound iodine in cases of chronic simple glaucoma as compared with those with closed-angle glaucoma.

These results are surprisingly consistent but so far unexplained, though some of the series are small, and further independent data are needed. Several studies have also been made on the ABO blood groups of small numbers of patients who suffer from glaucoma. The overall results show a greater relative frequency of A than of B and O. A single study of only 100 mixed cases of glaucoma shows a marked deficiency of ABH secretors.

This brief summary of the associations of glau-

coma and genetic polymorphisms indicates the probability that one or more of the commonly studied human polymorphisms contribute to the polygenic aetiology of the glaucomas. Clearly confirmatory studies should be done using the 3 polymorphisms already investigated, but other associations should also be sought. The careful work reported in this issue by David and Jenkins is welcome. They sought associations with 13 polymorphisms in a series of 100 patients with primary chronic simple glaucoma. The results from such a small group, although inconclusive, will form a firm base for future investigations and should encourage others to collect and publish further data.

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Genetic markers in glaucoma

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SUMMARY A number of genetic polymorphisms have been investigated in Negro and Caucasoid patients with glaucoma and the results compared with data obtained on healthy controls. A sample of 61 Negro patients was not significantly different from a sample of 238 controls with respect to 18 red cell and serum protein systems; no association between glaucoma and any of these systems could be demonstrated. The comparison among Caucasoids, using 14 systems, was made between 31 patients and 70 controls. The populations differed from each other in the rhesus and Duffy blood group systems, and a significant association between open-angle glaucoma and rhesus D (+) was found.

It has been known for many years that primary open-angle glaucoma (OAG) occurs more frequently in families in which another relative suffers from the disease. A recent study found a 50% positive family history among patients with primary OAG.¹ And the sibs and offsprings of glaucoma patients have been shown to have an increased incidence of glaucoma.²⁻⁴

Throughout the years many features related to OAG have been found to be heritable. Among these are the increased cup/disc ratio,⁵ the height of the intraocular pressure,⁶ and the hypersensitivity to topically administered corticosteroids.⁷ The accepted view today concerning the mode of transmission of primary OAG is that it is multifactorially inherited,^{4,8} and various workers have looked for associations between genetic polymorphisms and OAG.⁹

The present study presents the results of genetic marker studies on patients with primary OAG drawn from 2 distinct population groups and compares them with healthy control samples.

Materials and methods

Sixty-one black patients and 31 white patients with OAG constitute the material for the study. All the patients were attending the glaucoma clinics at the Johannesburg General Hospital and at St John's Eye Hospital, Baragwanath. The control population

used for the black population was the Rural Pedi, which had been carefully selected for the International Biological Programme (Human Adaptability) by Jenkins.¹⁰ In the case of the newer polymorphisms other populations studied by the MRC Human Ecogenetics Unit were used. The Caucasoid patients were compared with a population sample of Johannesburg Afrikaans university student volunteers who are part of an ongoing study into the genetics of hyperlipidaemia.

Blood was collected by venepuncture into 2 Vacutainers, one containing ACD and one containing no anticoagulant, and tested for a wide range of genetic characters. Blood grouping was performed by standard methods recommended by Race and Sanger,¹¹ the red cell enzyme systems and haptoglobins and transferrins by the methods summarised by Giblett.¹² In addition glutamic pyruvic transaminase phenotypes were determined by the method of Chen and Giblett,¹³ the esterase D by the method of Hopkinson *et al.*,¹⁴ the carbonic anhydrases by the method of Hopkinson *et al.*,¹⁵ and glyoxalase I by the method of Komph *et al.*¹⁶

Phenotype differences between the population with the disease and the control population were assessed by means of the χ^2 test. The method of Woolf¹⁷ as modified by Haldane¹⁸ was used to assess the significance of the association between a genetic character and the disease.

Results and discussion

The phenotypes among the black glaucoma patients and their normal controls are set out in Tables 1

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and 2. No polymorphism was encountered in the adenosine deaminase system (the ADA² allele attains very low frequencies in Southern African Negroids) and in the haemoglobins, though one individual was found to have the δ -chain variant, HbA₂' or HbB₂. (The gene for HbA₂' attains low frequencies in most Southern African populations and it is polymorphic among the Herero of South West Africa/Namibia and the Kgalagadi of Botswana (unpublished data).)

It will be seen that no significant differences could be found in the ABO, MNS, rhesus, Kell, Duffy, 6-phosphogluconate dehydrogenase (6PGD), adenylate kinase (AK), phosphoglucomutase (first and second loci) (PGM₁ and PGM₂), acid phosphatase (AcPh), peptidase A (PepA), glutamic pyruvate transaminase (GPT), glyoxalase (GLOI), carbonic anhydrase I and II (CA_I and CA_{II}), esterase D (EsD), haptoglobin (Hp) and transferrin (Tf) systems. There seemed to be an excess of glucose 6-phosphate dehydrogenase (G6PD) deficient individuals (Gd(-), A-) among the glaucoma patients, but it did not attain significance ($P > 0.05$).

The same range of investigations was carried out on Caucasian patients suffering from glaucoma and the results compared with a normal control population (Tables 3 and 4). Significant differences

Table 1 Comparison of ABO, rhesus and MNSs blood groups among Negro glaucoma patients and healthy control population

System and phenotype	Glaucoma patients	Controls	χ^2	DF	P
ABO	(n=61)	(n=238)			
A ₁	9	35	3.87	2	>0.50
A ₂	7*	26			
Abantu	3	4			
B	11	42			
AB	3†	7			
O	28	123			
Rhesus	(n=61)	(n=237)			
ccDee	45	155	12.492	6	>0.50
CcDee	3	39			
ccDEe	9	33			
CCDee	1	0			
ccDEE	2	2			
ccdee	1	6			
CcDEe	0	2			
MNSs**	(n=59)	(n=130)			
MMS	8	18	3.862	5	>0.50
MMss	10	11			
MNS	14	27			
MNnn	17	48			
NNS	2	7			
NNss	8	19			

*Three were A₁B₂. †Two were A₂B. **Tested with anti-M, -N, and -S sera only. ‡There were 2 (3.4%) Henshaw positives among the glaucoma patients: 1 MMS and 1 MNS; among the controls there were 6 (4.6%): 2 MMS and 4 MNS.

Table 2 Comparison of Kell and Duffy blood group systems, as well as red cell enzymes glucose 6-phosphate dehydrogenase (G6PD), 6-phosphogluconate dehydrogenase (6PGD), adenylate kinase (AK), glutamic pyruvate transaminase (GPT), esterase D (EsD), phosphoglucomutase, first locus (PGM₁) and second locus (PGM₂), peptidase A (PepA), red cell acid phosphatase (AcPh), carbonic anhydrase, second locus (CA_{II}), glyoxalase I (GLOI); and the serum proteins haptoglobins (Hp), and transferrins (Tf) among Negro glaucoma patients and a healthy control population

System and phenotype	Glaucoma patients	Controls	χ^2	DF	P
Kell	(+) (-)	0 130			
Duffy	a+b- a-b+ a-b-	11 4 119	1.827	1	0.10
G6PD**	B A A-	67 14 3	4.561	2	<0.05 <0.10
6PGD	A AC C	71 7 2	1.581	1	0.10
AK	1 2-1	85 3	0.275	2	>0.80
GPT	1 2-1 2	75 23 0	2.485	2	>0.20
EsD	1 2-1 2	88 7 2	1.260	2	>0.50
PGM ₁ †	1 2-1 2	73 33 3	1.742	2	>0.30
PGM ₂	1 2-1	105 5	1.018	1	>0.20
PepA	1 2-1 8-2 2	249 50 0 4	1.008*	3	>0.70
AcPh	B AB A RB RA R	54 14 0 5 3 0	5.092	5	>0.30
CA _{II}	1 2-1 2	81 16 1	3.694	2	>0.10
GLO I	1 2-1 2	14 38 46	0.813	2	>0.50
Hp	1 2-1 2-1 mod 2 O	22 25 4 23 2	4.24	4	>0.30
Tf	C CD	182 15	0.079	1	>0.70

*Obtained by pooling PepA 8-2 and PepA 2 categories; control population from Kirk *et al.* **Males only. †Excluding one individual from control population who was PGM₁ 6-1.

Table 3 Comparison of ABO, rhesus, and MNSs blood groups among Caucasoid glaucoma patients and a healthy control population

System and phenotype	Glaucoma patients (n=31)	Controls (n=70)	χ^2	DF	P
ABO					
A ₁	9	21	0.878	5	>0.95
A ₂	3†	10			
B	3	11			
AB	1*	3††			
O	13	25			
Rhesus**					
CcDee	5	26	25.326	6	<0.001
ccdee	0	13			
CcDEe	6	10			
ccDEe	3	9			
CCDEe	13	5			
ccDEE	3	5			
ccDee	0	2			
MNSs					
MMS	3	7	12.566	5	<0.05 >0.02
MMss	1	7			
MNS	12	23			
MNss	12	15			
NNs	0	7			
NNss	3	11			

†Two individuals were A₁st. *This individual was A₂B. ††One A₁B and two A₂B. **When Rhesus negative (ccdee) compared χ^2 (DF=1) = 3.404; 0.10 > P > 0.05.

were apparent with respect to 2 systems: Duffy (P<0.01), because of a striking deficiency of Fy(a+b+) and excess of Fy(a+b-) and Fy(a-b-) individuals among the OAG patients when compared with controls; and in the rhesus system (P<0.001), where the difference was due to a striking excess of CCDee and a decrease of CcDee individuals among the OAG patients. Equally striking is the absence of Rh negative (ccdee) individuals among the OAG patients when compared with the controls, but the difference just fails to reach significance (0.02 < P < 0.05).

There have been relatively few studies of the association of genetic polymorphic characters with glaucoma. Mourant *et al.*⁹ have recently summarised them. In the ABO system there appeared to be an excess of A over O [χ^2 (DF=1)=6.6127] but not of B over O [χ^2 (DF=1)=0.0164] in a pooled series representing 336 patients from 5 different studies. One Indian population (from Sitapur, North India) was studied for ABH secretor status, and there was a striking deficiency of secretors among a group of 56 wide-angle, 39 narrow-angle, and 5 unclassified cases of primary glaucoma when compared with controls [χ^2 (DF=1)=50.884]. In the phenylthiocarbamide tasting system 7 studies, when combined, gave an excess of nontasters among OAG when compared with normal control

populations [χ^2 (DF=1)=46.5]. Two studies not included in Mourant *et al.*'s book are known to us: Kubickova *et al.*¹⁹ found an increased association of OAG with blood group O, and Arezzi²⁰ found the association to be with blood group A. In neither study was statistical significance attained.

The association between OAG and the various polymorphic characters in the Negro and Caucasoid populations are shown in Table 5. It will be seen that a significant departure of the relative incidence from unity is obtained in the rhesus system among the Caucasoids: there is an absence of rhesus D(+) individuals among the glaucoma patients [χ^2 (DF=1)=6.4805; 0.01 < P < 0.02]. There is a suggestion of

Table 4 Comparison of Kell, Duffy, and P blood group systems as well as red cell enzymes 6 phosphogluconate dehydrogenase (6PGD), adenylate kinase (AK), adenosine deaminase (ADA), glutamic pyruvate transaminase (GPT), esterase D (EsD), phosphoglucomutase, first locus (PGM₁), peptidase A (PepA), and acid phosphatase (AcPh) among Caucasoid glaucoma patients and a healthy control population

System and phenotype	Glaucoma patients (n=31)	Controls (n=70)	χ^2	DF	P
Kell	(+)	2	0.627	1	>0.30
	(-)	29			
Duffy	a+b+	7	12.438	3	<0.01
	a+b-	13			
	a-b+	7			
	a-b-	4			
P ₁	(+)	28	4.965	1	>0.02 <0.05
	(-)	3			
6PGD	A	29	0.322	1	>0.50
	AC	2			
AK	1	30	0.250	1	>0.50
	2-1	1			
ADA	1	27	2.356	2	>0.30
	2-1	3			
	2	1			
GPT	1	8	5.995	2	>0.05
	2-1	19			
	2	4			
EsD	1	26	3.040	2	>0.20
	2-1	5			
	2	0			
PGM ₁	1	19	4.253	2	>0.10
	2-1	8			
	2	4			
PepA	1	31	1.766	1	>0.10
	2-1	0			
AcPh	B	11	8.576	4	>0.50
	AB	13			
	A	3			
	CB	1			
	CA	3			

Table 5 Associations between glaucoma and various polymorphisms in the Negro and Caucasoid populations (see text for statistical method used)

System and association tested	Negro		Caucasoid	
	Relative incidence	$\chi^2(DF=1)$ for difference from unity	Relative incidence	$\chi^2(DF=1)$ for difference from unity
ABO				
A/O	1.2901	0.6017	0.7496	0.3810
B/O	1.1726	0.1696	0.5749	0.6915
MNSs				
NNS/other phenotype	0.7159	0.2310	0.1344	3.4370
MMss/other phenotypes	2.2042	3.0972	0.4164	1.1407
Rhesus				
D+/D-	1.1325	0.0233	14.7900	6.4805*
Kell				
K+/K-			0.6231	0.4534
Duffy				
Fy(a+)/Fy(a-)	0.4366	1.5550	0.8819	0.0816
P				
(P ₁ (+)/P ₁ (-))			3.5368	4.5539
G6PD				
GdA-/GdB+ GdA	3.8230	3.9243		
6PGD				
6PGD (C/6PGD A+6PGD AC	1.5243	0.2544		
PGM ₁				
PGM ₁ 2/PGM ₁ 1 + PGM ₁ 2-1	3.3810	2.7449	4.4836	3.8580
Ac Phosphatase				
AcPh B/other phenotypes	0.9633	0.0095	0.7449	0.4623
Carbonic anhydrase II				
CA ₁₁ 2/CA ₁₁ 1 + CA ₁₁ 2-1	3.1553	1.5306		
Glyoxalase I				
GLO2/GLO1 + GLO2-1	1.2621	0.4310		
Haptoglobins				
Hp2/Hp1 + Hp2-1 + Hp2-1m	1.2574	0.3526		

*0.01 < P < 0.02.

association in the case of G6PD among the Negro patients and in the case of PGM₁ among the Caucasoid patients. No confirmation has been found for the observation by Arezzi²⁰ and Kubickova *et al.*¹⁹ for a greater prevalence of glaucoma among blood group A subjects, or for the observation by Kubickova *et al.*¹⁹ of an association with group O.

It is well known that the carbonic anhydrase inhibitors such as acetazolamide or methazolamide are the only diuretic agents of value in reducing

aqueous formation in patients with glaucoma and, hence, in daily use in the treatment of the disease. It was of some interest, therefore, to find a decreased proportion of CA₁₁2-1 heterozygotes among the black glaucoma patients when compared with the control group. This difference did not, however, attain significance ($P > 0.10$), and a comparison of relative incidence of CA₁₁2 with the other CA₁₁ phenotypes failed to reveal a significant association [$\chi^2(DF=1)=1.5306$].

Mourant *et al.*'s⁹ very useful summary failed to show any association between glaucoma and the MN and rhesus blood group systems or haptoglobins. They drew attention to one study, that of Garg and Pahwa,²¹ which revealed an association between glaucoma and nonsecretors of ABH. They could locate 7 studies, representing a total of 746 cases, and association between PTC taste testing and OAG which revealed a raised frequency of nontasters in both Caucasoids and Negroids.

With the advent of tissue typing several investigations were carried out to study the association between the HLA antigens and OAG. At this stage, the reports in the literature are rather conflicting,²²⁻²⁵ and more research is needed before a meaningful conclusion with regard to this polymorphism can be reached.

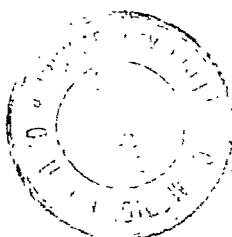
We are not aware of any studies directed towards establishing association between OAG and the other serological polymorphisms, many of which have been included in the present study. We present our findings in detail in the hope that other workers might be encouraged to extend the search, pooling our results with theirs and in this way, hopefully, discovering the associations which might well exist.

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The optic disc in glaucoma. IV: Optic disc evaluation in the ocular hypertensive patient

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SUMMARY A prospective study was carried out over a 3-year period on patients with one normotensive eye and one eye with ocular hypertension. A greater variability in the responses to visual field testing was apparent in the hypertensive eye, but only on comparison of serial visual fields. Analysis of the stereo disc photographs demonstrated larger cup to disc ratios in the hypertensive eye without changes in the nerve fibre layer to equate with the visual field response. Stereo disc photography is a quick and simple method of recording changes in the optic disc and should be considered in the follow-up of ocular hypertensive patients.

The incidence of ocular hypertension (an intraocular pressure >21 mmHg without visual field defects and glaucomatous cupping) far exceeds the incidence of glaucoma. Actuarial analysis¹ and long-term follow up studies of ocular hypertensives^{2,3} suggest that a large proportion of eyes with an intraocular pressure >21 mmHg without other signs of glaucoma will not progress to develop the disease ($>50\%$ in 15 years according to Sorensen *et al.*³). The decision on which patient with ocular hypertension alone requires treatment must therefore be based on factors other than recognition of elevated intraocular pressure. These factors may be grouped. Firstly, the existence of so-called *high risk factors*, found in a larger proportion of glaucoma patients than normals, such as a Po/C >100 after water drinking,⁴ high myopia,⁵ diabetes,⁶ and a positive family history.⁷ However, these high-risk factors *do* occur in the normal population, and, in view of the relatively low prevalence of glaucoma, the chances are that for any individual discovered to have a high-risk factor he will not have glaucoma.

Secondly, *predictive factors* have been investigated to see whether any one is especially linked to the future development of glaucoma. If the initial intraocular pressure exceeds 30 mmHg, then the chances of eventual field defects developing are quite high (7 out of 17 in 5 years,⁸ 2 out of 8 in 9 years,⁹ and 5 out of 17 in 5 years¹⁰). However, many eyes have been shown in prospective studies to develop field defects despite an initial intraocular

pressure of below 30 mmHg. Other predictive factors that have failed to stand the test of a prospective study have included Po/C 100^{9,11} and an initial C/D ratio >0.5 .^{9,12}

Lastly, several biochemical and other *markers* for chronic simple glaucoma have been suggested. All have had doubts cast upon their usefulness. For example, steroid responsiveness,^{9,13} HLA typing,¹⁴ and the response to topical epinephrine.¹⁵

In the absence of any test or group of tests that would allow identification of the future glaucoma patient from a group of ocular hypertensives the clinician needs to resort to long-term follow-up. Several authors have commented on changes in visual function or fundal appearance in the ocular hypertensive. Fishman¹⁶ noted, and Portnoy¹⁷ measured, optic disc (cup) asymmetry in ocular hypertensives while Sommer *et al.*¹⁸ demonstrated defects in the retinal nerve fibre bundle layer in the eyes of patients who subsequently developed glaucomatous visual field defects. Werner and Drance¹⁹ detected 'localised minor disturbances' on visual field testing at the site of a later developing visual field defect. Lakowski *et al.*²⁰ found higher 100 hue scores in ocular hypertensive patients than normal persons.

Each of the above signs was assessed separately in different studies. To try and assess the relative incidence of these signs in ocular hypertensives the authors selected a group of patients with unocular hypertension. These patients were entered into a prospective study and followed over a 3-year period. During that time tests of visual function and observations of fundal appearances were made.

Patients and methods

Patients were entered into the study if, over a 6-month period, the intraocular pressure in one eye was consistently above 21 mmHg and in the other eye consistently below 21 mmHg, together with a normal 3 isopter Goldmann field²¹ and if the eyes were without evidence for other ocular disease. Ten patients fulfilled these criteria.

Patients were seen every 6 months for an initial 12-month period. At each visit the following tests were performed: intraocular pressure check by applanation tonometry, visual fields testing by Friedmann analyser, mydriasis and slit-lamp funduscopy followed by stereodisc photography using colour film with a $\times 2$ adaptor. The stereoscopic effect was obtained by standard movement of the optic disc within the grid of the objective lens.²² Care was taken to focus on the nerve fibre layer.

At the end of the 12-month follow-up period visual field testing was supplemented by static field testing on the Tubingen Oculus Perimeter. The patients attended on 2 separate days for the visual field test. At the time of the first visit an initial measurement was made of the intraocular pressure and the pupils were dilated with cyclopentolate 1% and phenylephrine 10%; central visual field analysis was performed. The photopic static cuts were performed in a standard manner,²³ a single radial 'cut' being made in each quadrant. Finally a peripheral field was obtained and the intraocular pressures measured. At the time of the second visit the pupils were again dilated and the patient dark-adapted for 30 minutes. An analysis of the scotopic field was made. On this occasion the patient fixed on a red 10° fixation target of minimum illumination that could be comfortably seen. The test target was 104 seconds in diameter presented for 1/10th of a second. The threshold of every 4th degree from 1° through 25° was assessed, followed by the threshold of every 4th degree from 23° to 3°. The macular sensitivity was checked 3 times with a 42° target. Finally a Friedmann field analysis was performed, the threshold for each patient being found.

These static perimetric examinations were performed every six months for an 18–24-month period, a minimum of 2 (1 patient) and a maximum of 4 (1 patient) such tests were performed.

The optic disc photographs were collected at the end of the 3-year period and examined by the writers in 3 ways, on each occasion without the name of the patient or the hypertensive eye being known. Firstly, the disc photographs were presented in sequence for each eye and examined for changes in the visibility of the nerve fibre layer, the dimensions of the cup orifice, and the shape of the optic cup.²²

Secondly, the photographs were presented as stereo pairs of the 2 eyes of each patient to compare the C/D ratio, the cup volume, and the visibility of the nerve fibre layer of the 2 eyes. Thirdly, black-and-white prints were made from the photographs taken of each patient at the time of the last visit. After the configuration of the cup orifice had been checked with the corresponding stereo disc photographs a pencil line was drawn round the margin of the optic cup and the optic disc allowing a numerical value for the C/D ratio to be obtained.²⁴ This numerical value for the C/D ratio was compared for the 2 eyes of each patient. Finally, the photographs were identified, with the name of the patient and the hypertensive eye being noted.

Results

Of the 10 patients entered 1 died after 18 months and is not reported on here. The results are summarised in the tables. Table 1 shows the intraocular pressures during the period of study. The mean

Table 1 Intraocular pressure measurement

Patient no.		Mean IOP in first 12 months	Mean IOP in last 18–24 months					
			Premydriasis			Postmydriasis		
			IOP	SEM	No. observations	IOP	SEM	No. observations
1	R	27	28.3	± 1.16	8	24.9	± 1.02	8
	L	22.5	23.1	± 0.41		22.5	± 0.67	
2	R	28	19.6	± 1.8	9	24.6	± 0.26	9
	L	17	15.2	± 1.06		20.0	± 0.53	
3 ¹	R	32	26.3	± 1.5	9	31.0	± 0.83	9
	L	21.3	18.8	± 0.58		22.1	± 0.57	
4	R	16.3	17.8	± 0.7	4	20.3	± 2.1	4
	L	25	19.8	± 1.75		22.3	± 1.75	
5	R	28.5	22.6	± 1.04	10	34.0	± 2.34	10
	L	19.5	17.5	± 0.72		20.2	± 1.33	
6 ²	R	30.7	29.9	± 3.50	7	38.9	± 1.93	7
	L	18.3	21.3	± 0.30		22.3	± 0.60	
7 ³	R	50.0	20.9	± 0.38	9	22.8	± 0.63	9
	L	19	19.4	± 0.72		25.5	± 3.33	
8	R	18.7	19.5	± 0.42	9	28.3	± 4.6	9
	L	30.7	28.8	± 4.6		36.7	± 2.33	
9 ⁴	R	53.5	24.9	± 1.56	9	45.1	± 3.67	9
	L	22.5	16.9	± 0.76		20.0	± 0.73	

¹Presenting IOP <21 mmHg, subsequent IOP >21 mmHg. ²Progressive IOP rise required antiglaucoma treatment in the last 18 months.

³Presenting IOP 50 mmHg, subsequent R filter operation. ⁴Progressive IOP rise required antiglaucoma treatment to R eye throughout.

Table 2 *Results of visual field testing*

Patient no.	No. of times tests performed	Hypertensive eye	Tested eye	Sensitivity reduction in one or more quadrants			
				Photopic cuts	Scotopic field	Friedmann	Peripheral isopter
1	3	R	R	UT sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	LT sens. decr. $\frac{1}{2}$	UT sens. decr. $\frac{1}{2}$	NAD
			L	UT sens. decr. $\frac{1}{2}$	NAD	NAD	NAD
2	3	R	R	UT sens. decr. $\frac{1}{2}$ UN sens. decr. $\frac{1}{2}$	NAD	Sens. decr. $\frac{1}{2}$	NAD
			L	NAD	NAD	Sens. decr. $\frac{1}{2}$	NAD
3	3	R	R	UR sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	Sens. decr. $\frac{1}{2}$ Sens. incr. $\frac{1}{2}$	UT sens. decr. $\frac{1}{2}$	NAD
			L	NAD	NAD	NAD	NAD
4	2	L	R	UT sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$ LN sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	NAD NAD	UN sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	NAD
				L	NAD	NAD	NAD
5	4	R	R	UT sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	UN sens. incr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	LT sens. decr. $\frac{1}{2}$ UT sens. decr. $\frac{1}{2}$	NAD
			L	NAD	Sens. incr. $\frac{1}{2}$	LT sens. decr. $\frac{1}{2}$ LN sens. decr. $\frac{1}{2}$	NAD
6	3	R	R	UT sens. decr. $\frac{1}{2}$ UN sens. decr. $\frac{1}{2}$ LT sens. decr. $\frac{1}{2}$	UT sens. decr. $\frac{1}{2}$ LN sens. decr. $\frac{1}{2}$	UT sens. decr. $\frac{1}{2}$ UT sens. decr. $\frac{1}{2}$	Variable $\frac{1}{2}$
				L	LN sens. decr. $\frac{1}{2}$	UT sens. decr. $\frac{1}{2}$	
7	3	R	R	UT sens. decr. 3/3 UN sens. decr. 3/3 LT sens. decr. 3/3 LN sens. decr. 3/3	UT sens. decr. 3/3 UN sens. decr. 3/3 LT sens. decr. 3/3 LN sens. decr. 3/3	UN sens. decr. 3/3	UN field defect 3/3
			L	UT sens. decr. $\frac{1}{2}$	NAD	NAD	NAD
8	3	L	R	NAD	NAD	NAD	NAD
			L	UN sens. decr. $\frac{1}{2}$ UT sens. decr. $\frac{1}{2}$ LT sens. decr. 2/3 Cen. sens. decr. 2/3	Sens. decr. 3/3	UT sens. decr. 2/3	NAD
9	3	R	R	UN sens. decr. 2/3 UT sens. decr. 2/3 LN sens. decr. 2/3 LT sens. decr. 2/3 Cen. sens. decr. 1/3	UT sens. decr. 1/3 LT sens. decr. 1/3	UN sens. decr. 1/3 UT sens. decr. 1/3	Constricted 1/3
			L	LT sens. incr. 1/3	UT sens. decr. 1/3	UT sens. decr. 2/3 UN sens. decr. 2/3	NAD

UT=upper temporal, UN=upper nasal, Sens.=sensitivity, Decr.=decreased, Incr.=increased, LT=lower temporal, LN=lower nasal, Cen.=central, Numerator=no. times reduced sensitivity, Denominator=no. times tested.

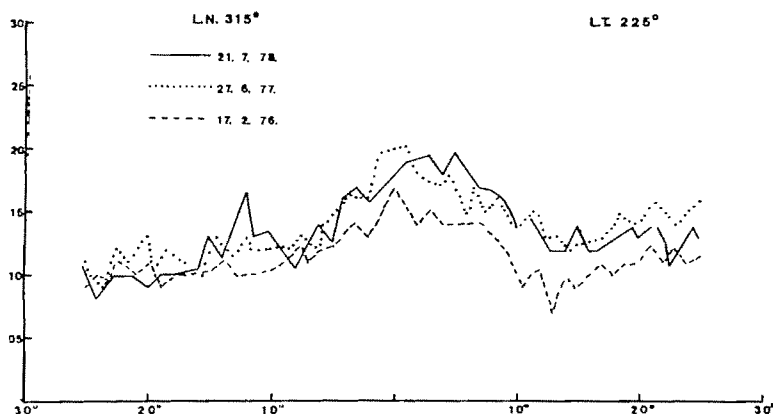


Fig. 1 Photopic static perimetric fields from normotensive left eye of patient 6 illustrating depression of lower temporal field.

intraocular pressures are given for the first 12 months. Patient no. 7 developed a permanent visual field defect and eventually required filtration surgery. The visual field and optic disc results for this patient are presented as they form a useful comparison with the other, ocular hypertensive, patients. Three patients (nos. 1, 3, and 9) ran occasional pressures greater than 21 mmHg in the 'normotensive' eye over the first 12 months, but there was always a minimum of 5 mmHg difference between the 2 eyes. Two patients (nos. 6 and 9) required antiglaucoma treatment to lower the intraocular pressure from >40 mmHg to <30 mmHg during the trial.

The results of visual fields testing are seen in Table 2. The hypertensive eye for each patient can be seen on sequential field testing to have a far greater variability in response. Reduced sensitivity was considered present either if there was a localised depression greater than 0.5 log unit¹⁹ in one part of the visual field on photopic testing (Fig. 1) or generalised depression of the whole of one or more

radial cuts when compared with the corresponding quadrant of the opposite eye seen on scotopic testing (Fig. 2). Reduced sensitivity was not found to be associated with isolated episodes of marked ocular hypertension. With the exception of patient 7, who had frank glaucoma in one eye, no patient had a permanent alteration in visual field sensitivity during the period of study.

Most eyes showed an increase in intraocular pressure following mydriasis. In no case was this caused by angle closure.

The results of optic disc analysis are seen on Tables 3 and 4. Analysis of sequential disc photographs failed to show progressive change in any case. Comparison of stereo photographs of the 2 eyes for each patient showed the optic cup orifice and volume to be larger in the hypertensive eye (Table 3, Figs. 3 and 4). Quantitative measurement of the cup/disc ratio showed the hypertensive eye to have the larger C/D ratio in all but 2 patients (nos. 2 and 4, whose intraocular pressures reverted to normal). The C/D difference between the 2 eyes

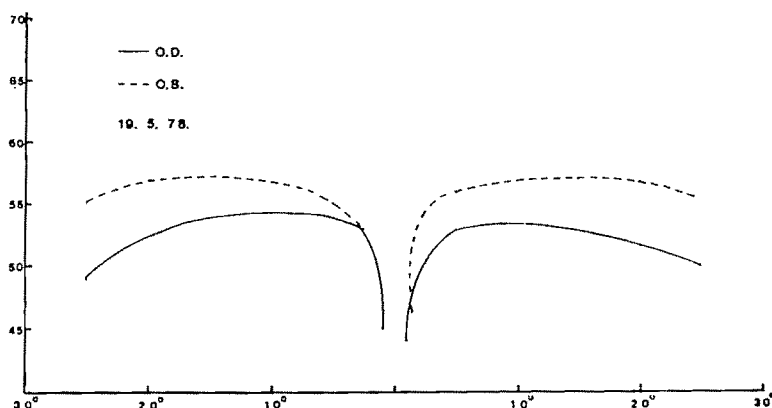


Fig. 2 Scotopic static perimetric fields showing generalised depression of the visual field in the hypertensive right eye of patient 3. Note: Oculus perimetric fields are shown: vertical axis represents logarithmic changes in target luminosity. Horizontal axis represents degrees either side of fixation.

ranged from 0.07 to 0.53, while the percentage increase in C/D ratio of the hypertensive eye compared with the normotensive eye ranged from 16% to 170%. The results of 100 hue testing are seen on Table 4. The patients in this study failed to give consistently higher 100 hue scores in the hypertensive eye.

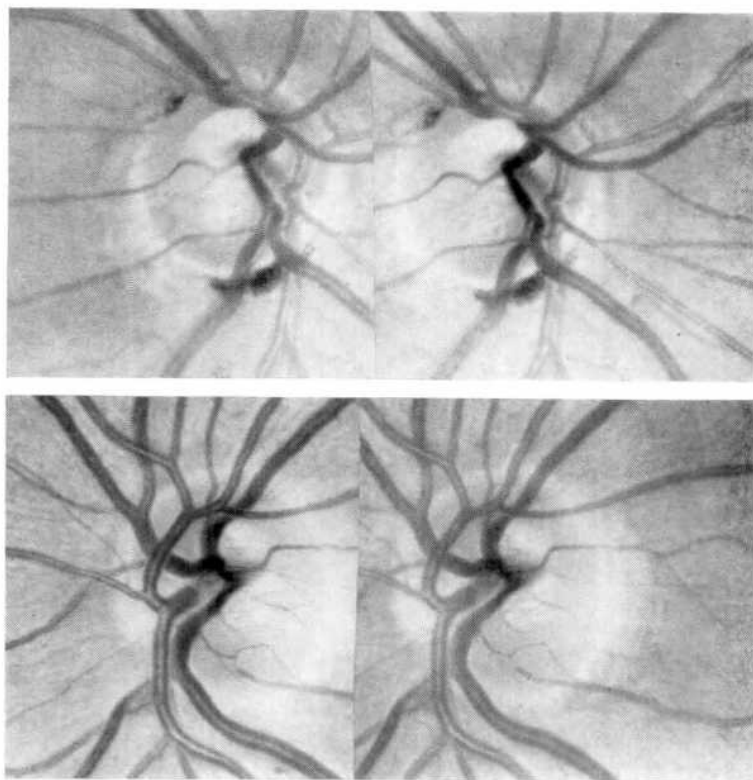
Table 3 *Results of subjective optic disc analysis*

Patient no.	Hypertensive eye	C/D ratio	Cup volume	Visibility nerve fibre layer
1	R	R>L	R>L	Visible R & L
2	R	R>L	R>L	Visible R & L
3	R	R>L	R>L	Visible R & L
4	L	R=L	R=L	Visible R & L
5	R	R>L	R>L	Visible R & L
6	R	R>L	R>L	Visible R & L
7	R	R>L	R>L	Invisible R Visible L
8	L	R=L	R=L	Invisible R&L
9	R	R>L	R>L	Invisible R&L

Table 4 *Vertical C/D ratio and hundred hue response versus intraocular pressure*

Patient no.	Eye	Mean IOP over last 18 months	Vertical C/D ratio	Difference R & L	Hundred hue
1	R	28.0	0.60	0.16	77
	L	23.1	0.44		42
2	R	19.6	0.43	0.02	11
	L	15.2	0.41		32
3	R	26.3	0.57	0.21	105
	L	18.8	0.36		116
4	R	17.8	0.21	0.06	44
	L	19.8	0.27		44
5	R	22.6	0.45	0.16	77
	L	17.5	0.29		81
6	R	29.9	0.72	0.21	129
	L	21.3	0.51		65
7	R	20.9	0.84	0.53	—
	L	19.4	0.31		—
8	R	19.5	0.43	0.07	374
	L	28.8	0.50		323
9	R	24.9	0.29	0.12	634
	L	16.9	0.17		374

Fig. 3 *Stereo photographs of hypertensive and normotensive eye of patient 6.*



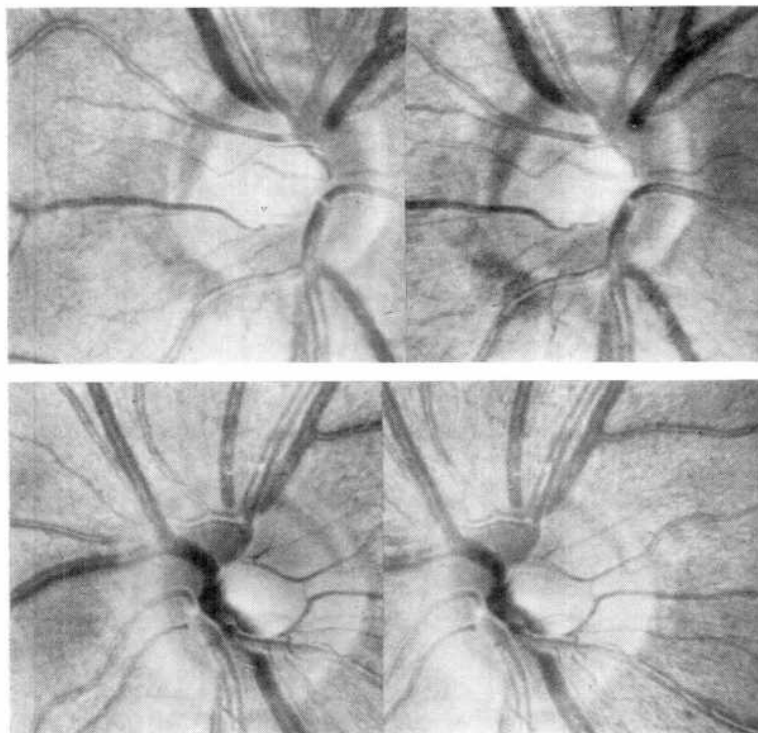


Fig. 4 Stereo photographs of hypertensive and normotensive eye of patient 2.

Discussion

The aim of any monitoring scheme for ocular hypertensive patients should be to use test methods that are accurate and reproducible. This study has compared a number of methods that could be so considered.

The patients tested in this study were entered on the basis of consistent ocular hypertension in one eye and consistently normal pressure in the second eye after they had been followed for a period of 6 months. As shown in Table 1, 2 patients (nos. 2 and 4) had mean intraocular pressures within normal limits for the last 18–24 months of the study, a finding not unexpected from the results of Sorenson *et al.*³ Secondly, patients 1 and 6 developed occasional intraocular pressures >21 mmHg during the last 18–24 months of the study, again a finding to be expected in any group of unocular hypertensives. It should be noted, however, that there was a consistent difference of >5 mmHg in the intraocular pressure between the 2 eyes in patients 1 and 6.

The results of the individual tests may be discussed separately.

SUBJECTIVE TESTING

Visual field. All patients had normal 3 isopter Goldmann and Friedmann field charts when entered

into the study. Patient 7 developed a consistent field defect within the first 12 months. The remaining patients had greater variability in response to visual field testing in the hypertensive eye (a feature noted by Werner and Drance¹⁹ as occurring prior to persistent field defects). This variability could be detected on photopic static Tübingen field and Friedmann field testing and to a less extent in scotopic static field testing, but not on assessing the peripheral field. It should be noted, however, that the variable responses were not consistently found in any one quadrant for a particular eye and that, while on one occasion a particular quadrant showed reduced or variable sensitivity, repeated testing gave normal responses for that quadrant but reduced sensitivity from another quadrant.

These variable responses were occasionally seen in the normotensive eye. It could *not* always be said, on the basis of a *single* visual field test, which eye was hypertensive for the patients in this study. Repeated visual field testing, however, clearly showed a greater incidence of variable responses in the hypertensive eye.

These results compare with the reproducible responses obtained on static testing of normal patients.^{19 25}

A careful check of the pre- and postmydriasis intraocular pressures at the time of visual field

testing could not relate reduced sensitivity to exceptionally high intraocular pressures for any patient (for it is known that elevating intraocular pressure produces, or increases the size of, visual field defects.¹⁹). In similar fashion the variable responses found by Donovan *et al.*²³ were not related to variations in intraocular pressure. While it is possible for the higher incidence of variable responses in the hypertensive eye to have been brought on by the higher postmydriasis pressures found on some occasions (Table 1), the highest recorded intraocular pressures were not always associated with the lowest retinal sensitivity.

Hundred hue. Hundred hue testing was not helpful in distinguishing between the 2 eyes for the patients in this series. This is in contrast to the results obtained by Lakowski²⁰ for groups of ocular hypertensives and normals. Despite the small size of the series here, direct comparison of 2 eyes should have indicated a consistently higher score in the hypertensive eye if this test was to have been of clinical use.

OBJECTIVE TESTING

Serial optic disc analysis. The fact that *no* change could be detected on analysis of the serial disc photographs may reflect only the short duration of the study. Patient 7, who was found to have a persistent visual field defect in the first 12 months of the study, had a localised notch in the neuro-retinal rim and no visible nerve fibres throughout the study. No patient was seen to develop slit-like defects in the nerve fibre layer.¹⁸

Comparison of paired stereo photographs from each patient. With the exception of patient 4, who was considered to have optic disc cups of equal size, the writers correctly identified the hypertensive eye as having the larger optic cup. The larger cup showed predominantly vertical elongation rather than overall enlargement (Fig. 3). There was no difference in the visibility of the nerve fibre layer between the 2 eyes except in patient 7.

Quantitative measurement of cup/disc ratios. The 2 eyes of a normotensive patient have optic cups that are very similar in size both in the size of the optic cup orifice¹⁶ and in the volume of the optic disc cup.¹⁷ This similarity in size reflects the similarity in size of the optic discs of any one patient. However, unequally sized optic discs have unequally sized optic cups.²⁶ Therefore in patients with slight dissimilarity in the size of the 2 optic discs a straight comparison of the optic cup sizes seen in the 2 eyes of any one patient might give a misleading impression of asymmetry and, from this, suggest an acquired change from elevated intraocular pressure. This appearance was seen in patient 2 (Fig. 4), who

was considered to have dissimilar cup/disc ratios in the 2 eyes on subjective analysis but who in fact had very similar cup to disc ratio in the 2 eyes. Because of these possible errors in subjective analysis, quantitative measurement of the C/D ratio and then comparison of the measurements obtained for the 2 eyes of each patient should be more accurate. The patients in this series were found to have a larger C/D ratio in the hypertensive eye (except in the 2 patients whose intraocular pressure reverted to normal during the study), making it likely that the difference between the C/D ratio in the eyes was an acquired change.

Conclusions

Hypertensive eyes in this study have been shown on visual field analysis to have variable responses on static field testing. These responses are similar to those noted by Werner and Drance¹⁹ to progress to permanent visual field defects, although there is no evidence that this change will occur for the eyes in this series. The greater variability in responses of the hypertensive eye was apparent only on serial visual field testing rather than on examination of the responses obtained at the time of a single visual field test. Subjective and quantitative assessment of C/D ratios demonstrated larger ratios in the hypertensive eye, but did not show changes in the nerve fibre layer to equate with the visual field response. Serial disc photography may need to be continued for more than 3 years before sequential changes become visible at the optic disc. Stereo disc photography was able to detect (presumed) change at the optic disc before permanent reduction in visual field could be detected. Stereo disc photography, as described, is a quick and simple method of documentation and should be considered for long term follow up of the ocular hypertensive patient.

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Timolol in operated closed-angle glaucoma

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SUMMARY Tonometry in 9 eyes (7 patients) provides some evidence that timolol eye drops are useful in improving control of pressure in eyes operated for closed-angle glaucoma. In cases 1 and 2 (Figs. 1 and 2) this beta 1 and 2 blocker reduced pressure consistently. Case 3 (Fig. 3) showed that timolol 0.5% twice daily was as effective as pilocarpine 2% or 4% with adrenaline 1%. The effect of timolol 0.5% in case 4 (Fig. 4) and case 6 (Fig. 6) was additive to pilocarpine and adrenaline; in case 5 (Fig. 5) it probably improved the effect of adrenaline, but in cases 4 and 5 there may have been some loss of effect with time. Case 7 (Fig. 7) showed a good effect of timolol, reversed on withdrawal, but pressure fell again in spite of continued withholding of timolol. Timolol will be especially valuable in the control of pressure if an operation involving iridectomy has not been completely successful in open-angle glaucoma or more especially in closed-angle glaucoma because it has no effect on the pupil. Miotics will tend to produce posterior pupillary synechiae because aqueous humour will go through the iridectomy, not under the edge of the pupil. The danger will be greater in eyes with closed-angle glaucoma because the pupil is closely applied to the anterior lens surface, which will also tend to produce irritative iridocyclitis.

In published work on the efficacy of timolol¹⁻⁷ or other beta-blockers⁸⁻¹⁹ in open-angle glaucoma it is curious that there seems to be no mention of its use for chronic closed-angle glaucoma which has not been controlled by operation involving an iridectomy or in which the patient has refused operation. Given (in the Bayesian sense) all the evidence of efficacy of timolol, especially that it very probably acts by reducing the rate of production of aqueous humour,²⁰⁻²² it would be reasonable to conclude that the drug would be effective in chronic closed-angle glaucoma if iridectomy or drainage operation has failed to control pressure satisfactorily; a similar argument would apply to cases of open-angle glaucoma with a failed drainage operation, to 'aphakic' glaucoma with or without a closed angle, 'pigmentary' glaucoma, low-tension glaucoma, or any form of 'secondary' glaucoma.

The following 7 patients are described to provide some support for the use of timolol in the control of cases of operated chronic closed-angle glaucoma. Such patients are not common, and it is hoped that a larger series over a longer period will be assembled to provide more definite evidence.

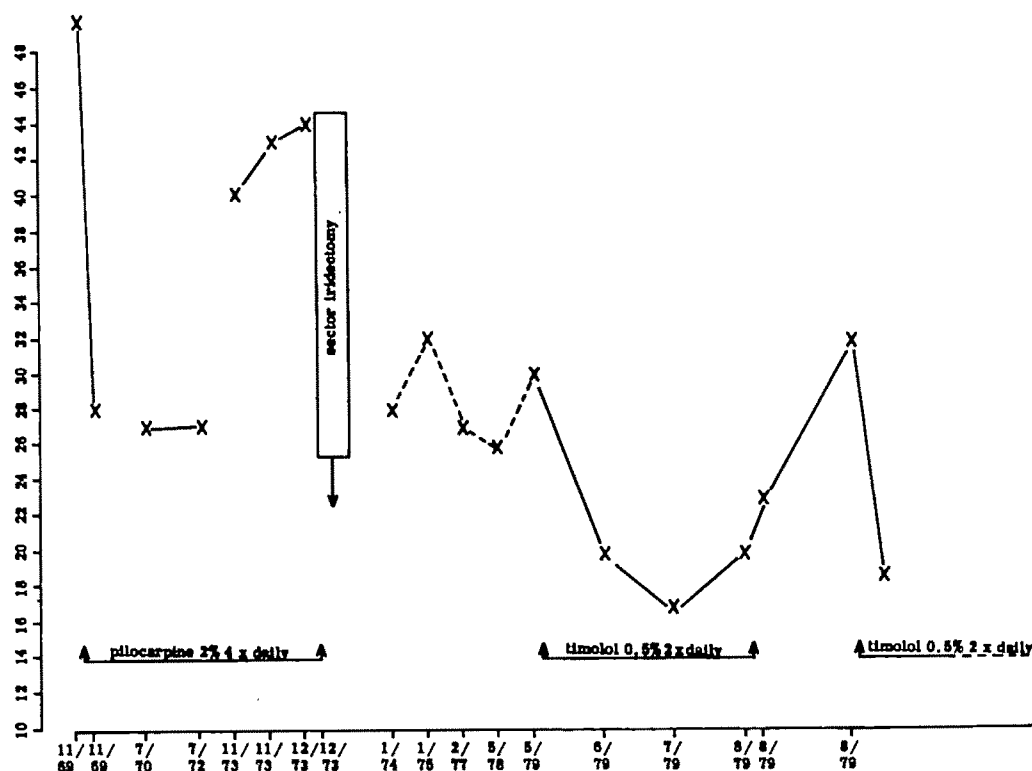
Patients and methods

Patients attending the glaucoma clinic for 'routine' monitoring of chronic closed-angle glaucoma following iridectomy or drainage operation were chosen. Timolol eye drops 0.25% or 0.5% were prescribed twice daily, usually in addition to pilocarpine $\pm$ adrenaline already being given. They were then asked to attend more frequently so that tonometric response to timolol could be assessed—at the same time of day as the pretimolol visits and tonometry. Applanation tonometry was done throughout by the same 3 glaucoma technicians. (Fields of vision were charted, and visual acuities etc. were also recorded at 4-6 monthly intervals.)

Results

Case 1 (Fig. 1) is the most convincing because he had a high pressure and no drug was used along with timolol in his right eye. (His left eye was predisposed to CAG and had had a successful peripheral iridectomy with normal visual acuity, discs, and pressure.) His right eye had lost all vision, with deep pathological cupping when he presented in 1969. Pilocarpine 2% 4 times daily reduced the tension for about 4 years, but it rose

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Figs. 1-7 Graphs of ocular tensions in cases of operated closed angle glaucoma in which additional medical treatment was judged advisable. Ordinates: mmHg (applanation). Abscissae (not to consistent scale) show month and year in which tonometry was done. See text for case histories. X = right eye, O = left eye.

again in 1973 when a sector iridectomy was done, in spite of the absence of vision, in order to delay degenerative changes. For about 5 years tension remained under or around 30 in a comfortable eye. Gonioscopy showed only 2/12 of the angle open. Timolol 0.5% reduced pressure to 20 or less for 3 months, but on withdrawal of treatment the pressure rose again; when the drug was recommenced a satisfactory response was again obtained. This patient will be continued on timolol indefinitely.

Case 2 (Fig. 2) has a lower pressure, but the results are reasonably convincing. He presented with bilateral subacute closed-angle glaucoma. (His left eye has had a successful sector iris inclusion which has controlled its pressure, with normal vision.) When the pressure in the right eye rose to 25 mmHg a few weeks after sector iridectomy, timolol was given and reduced the tension impressively. Gonioscopy showed 4/12 of the angle open. Subsequently the slight tendency for the pressure to rise again may be the result of, say, closure of

the limbal wound (though no bleb was seen) or a loss of effectivity of the drug. The pressure, however, rose further to 24 mmHg when the drug was stopped, but fell again when it was restarted.

Case 3 (Fig. 3) shows that timolol 0.5% twice daily is as effective as pilocarpine 2% or 4% with adrenaline 1% in the left eye. (The right eye had a successful sector iris inclusion in 1974 which has controlled tension, fields, and visual acuity.) A left sector iridectomy in 1974 seemed to require the addition of pilocarpine and adrenaline to control the tension. The angle was 4/12 open on gonioscopy. On withdrawal of all treatment pressure rose to 24 mmHg on 28 May 1979 but it fell to 19 or less for at least 3 months thereafter on timolol 0.5% twice daily.

Case 4 (Fig. 4) in spite of rather low pressure shows reasonably good evidence of an additive effect of timolol 0.5% to pilocarpine and adrenaline. Both the right (subacute CAG superimposed on chronic CAG with field loss) and left (subacute CAG) eyes responded dramatically well to pilo-

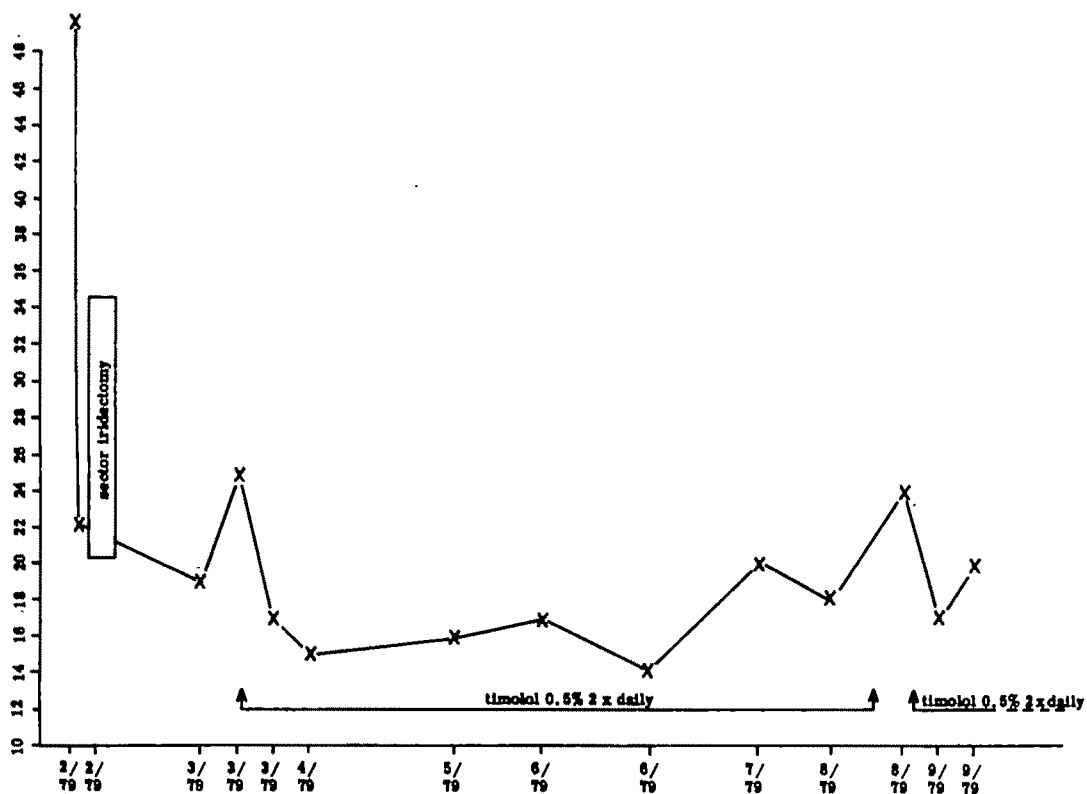


Fig. 2 See Fig. 1 for explanation.

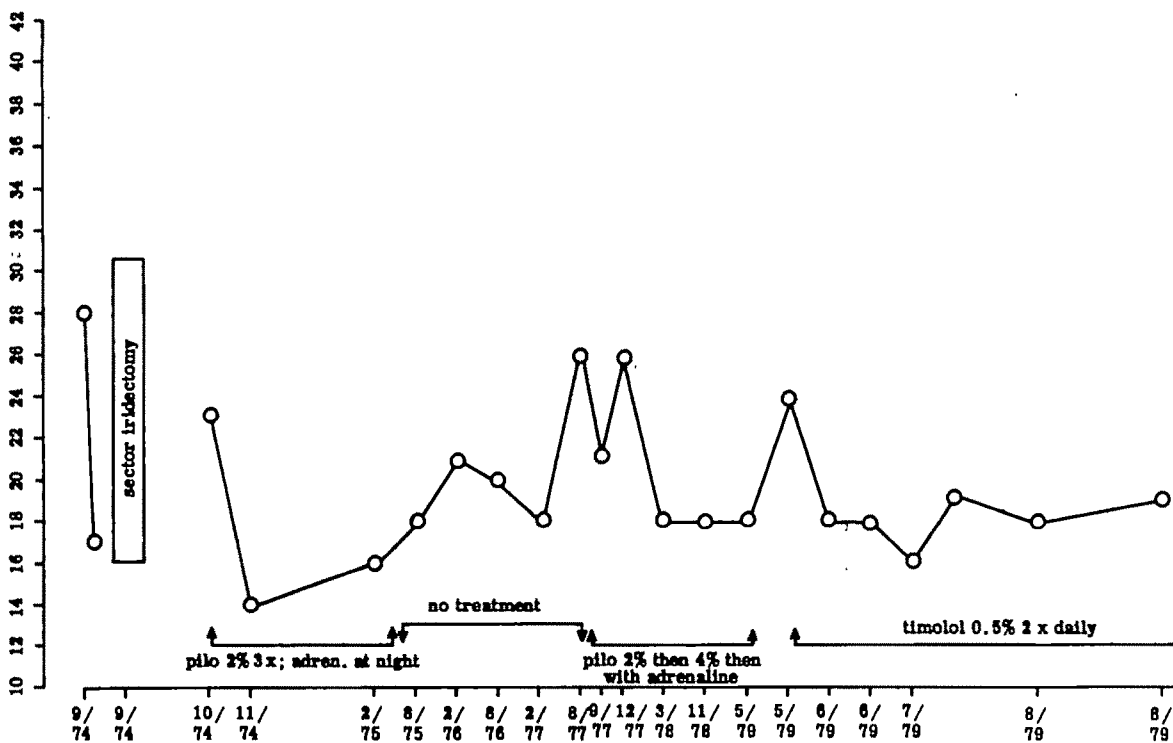


Fig. 3 See Fig. 1 for explanation.

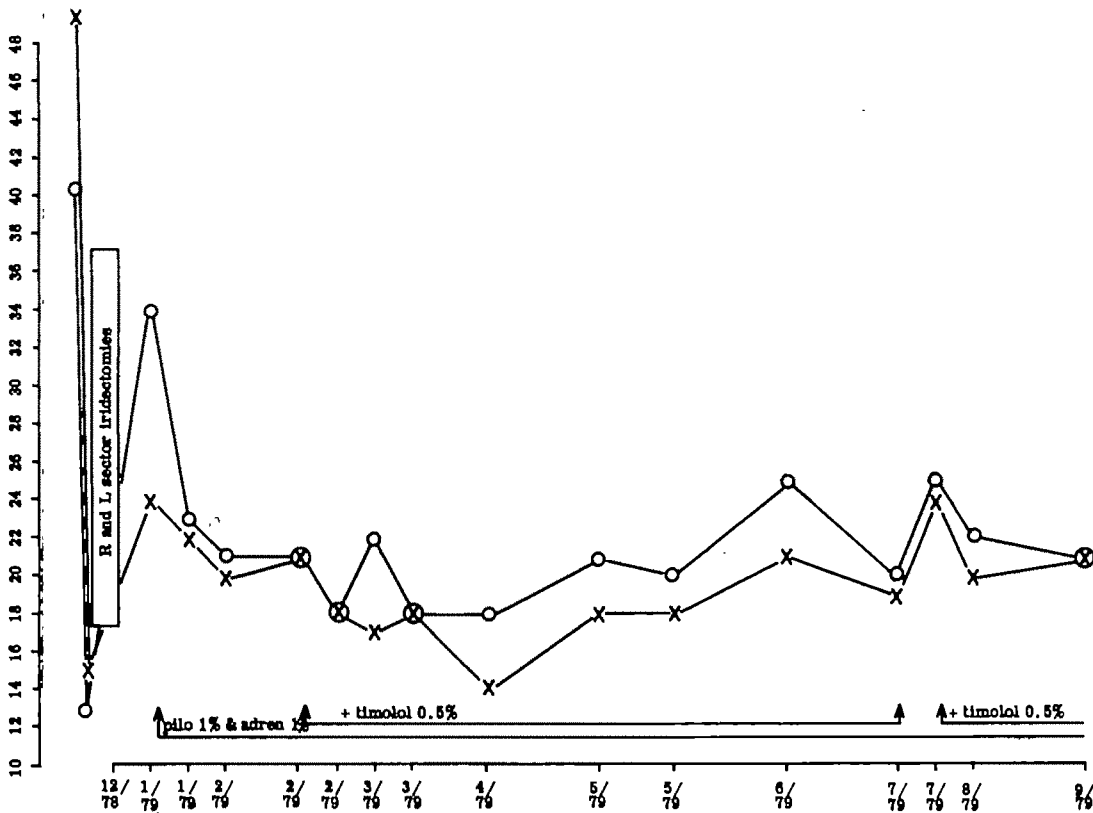


Fig. 4 See Fig. 1 for explanation.

carpine at presentation, so that bilateral sector iridectomies were done with an interval of 1 week between. A month later, however, pilocarpine and adrenaline were judged necessary and reduced pressures to just over 20 mmHg. The open 7/12 of the right angle was heavily pigmented; 5/12 of the open 10/12 of the left angle was also heavily pigmented. Timolol 0.5% was added twice daily to both eyes when it became available and seemed to reduce the pressure further. Any or all of the 3 drugs may have lost some effect as the pressure tended to rise during the next few months—or a late postoperative change may have occurred. However, withdrawal of timolol raised the pressure from R.19 and L.20 to R.24 and L.25 which was reversed when the drug was restarted.

Case 5 had bilateral peripheral iridectomies in 1954, but in 1977 pressures rose, so that adrenaline twice daily was given with reasonable control of pressure, probably improved by timolol 0.5% twice daily. Gonioscopy showed the right angle to be 5/12 open, and the left 4/12 open. Some loss of effect of timolol seems more likely than of adrena-

line by August 1979. Pressure rose slightly more when timolol was withdrawn, and reintroduction of timolol again seemed effective.

In case 6 (Fig. 6) the right eye (X—X) is included for completeness, though after its sector iridectomy the angle was completely open. The left eye showed poor control after a drainage operation, although the angle was 7/12 open. Pilocarpine and adrenaline obtained some reduction in pressure, which was considerably improved by added timolol 0.5% twice daily, albeit with some fluctuations. Withdrawal of timolol resulted in a rise of left pressure (not right, that eye being hardly glaucomatous, if at all), which was reversed when timolol was restarted.

Case 7 (Fig. 7) may not be justifiably included because in 1979 angles appeared open all round on gonioscopy (but see discussion). However, the right eye presented with acute CAG in 1963 for which an iris inclusion was done, followed in 1964 by a left peripheral iridectomy. Pilocarpine and adrenaline were used from 1968 to 1979. Timolol 0.5% twice daily was added and caused an impressive fall in tension in February 1979; during the

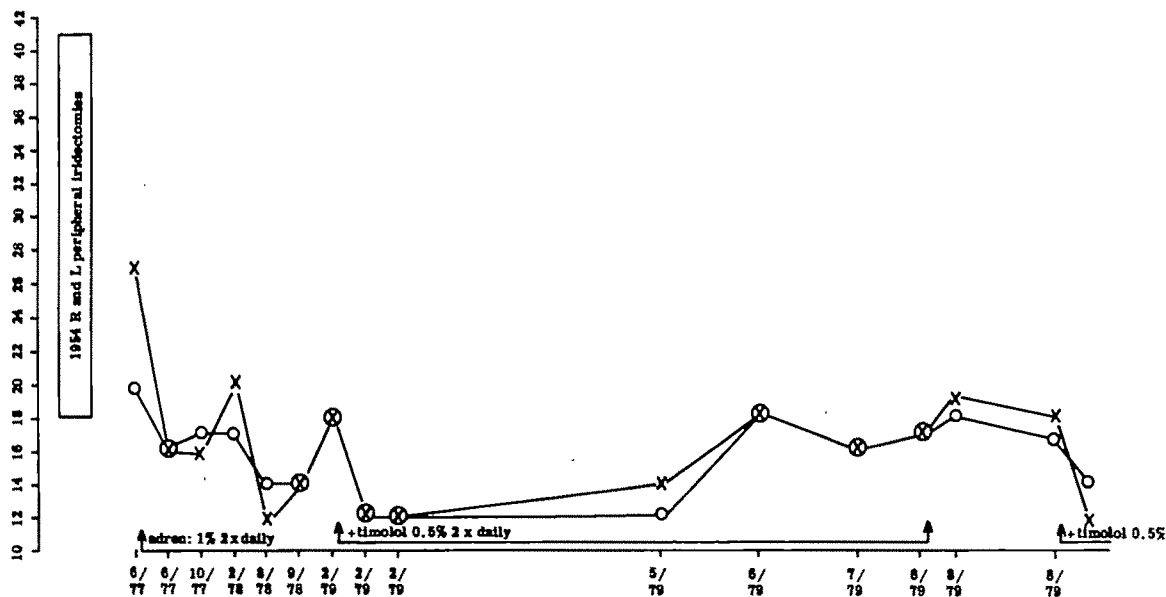


Fig. 5 See Fig. 1 for explanation.

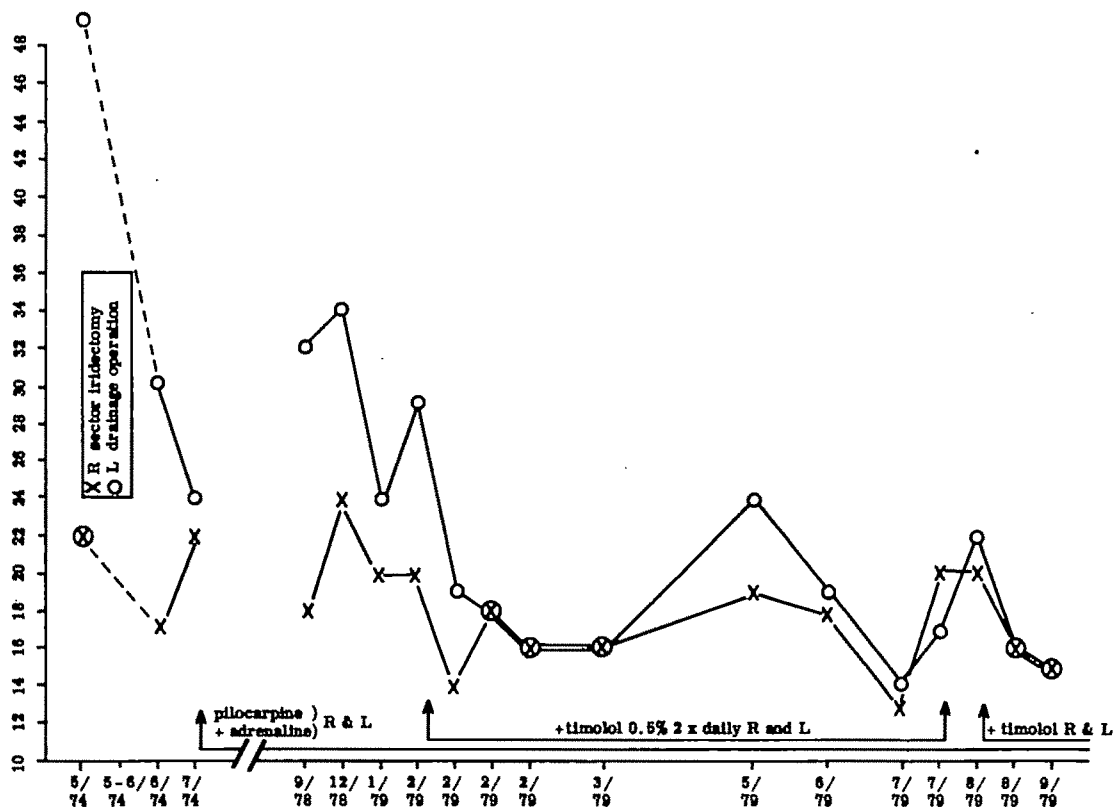


Fig. 6 See Fig. 1 for explanation.

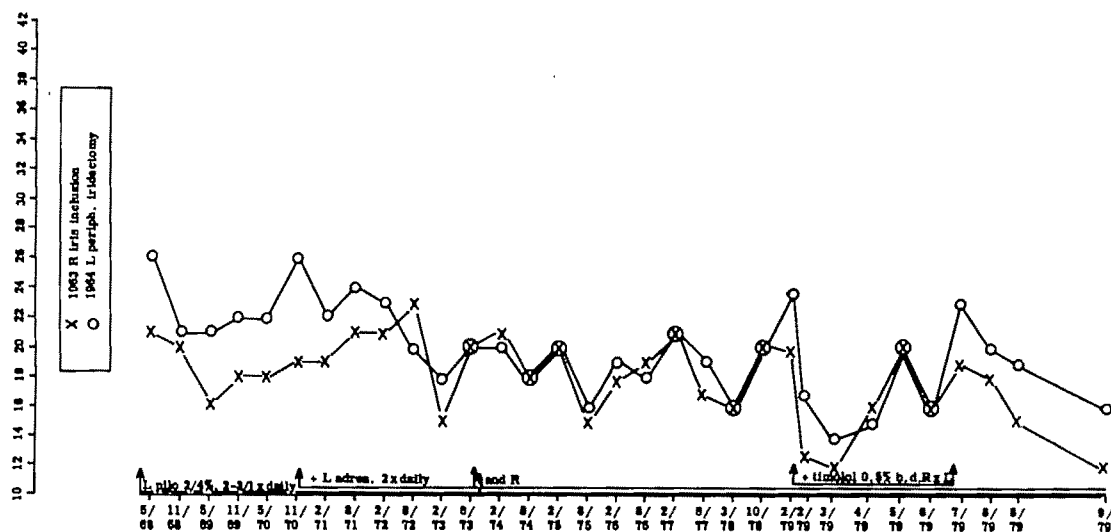


Fig. 7 See Fig. 1 for explanation.

next few months pressure rose again. Withdrawal of timolol, however, caused the pressure to rise further. It was decided to continue to withhold timolol, and, very surprisingly, pressure has fallen progressively: no satisfactory explanation seems available.

Discussion

It would be consistent with the known properties of timolol that it should be effective in cases of closed-angle glaucoma in which drainage operation or iridectomy had failed to control the pressure satisfactorily. That theoretical conclusion is supported by the evidence presented in the series of cases described in this paper. However, a double-blind controlled trial on a larger series would be preferable—but suitable patients are not common. Patients with chronic CAG or predisposed to CAG, who have refused operation, or patients for whom operation is not advisable for some reason, would also benefit from timolol (along with pilocarpine, of course) since reduced production of aqueous humour would reduce the ballooning of the iris and therefore open the angle.

Timolol is valuable for the medical treatment of open-angle glaucoma but is even more suitable for eyes which have had iridectomy ($\pm$ drainage operation) yet require medical treatment, especially in the case of CAG. After an iridectomy, peripheral or sector, presumably aqueous humour takes the path of least resistance, that is, does not pass under the pupil margin. Posterior synechiae are therefore

very likely to develop, especially of course if there is postoperative iridocyclitis. In eyes with CAG the pupil is more closely applied to the anterior lens surface than in eyes with OAG, so that posterior synechiae are more likely to develop in the former. *Miotics will aggravate this tendency* and may well in addition elicit some iritic response to mechanical trauma at the pupil, which would be an additional factor in production of synechiae. Pupillary synechiae will tend to produce occlusio pupillae and also cataract, especially when the pupil is small and its margin intact (as in case 7). (Adrenaline would not carry this risk, but significant pupil dilation even after iridectomy could compromise the narrow angle, as well as impose the optical disadvantages of mydriasis.) Accordingly, timolol is pre-eminently suited for control of pressure after an operation involving an iridectomy, both in OAG and especially in CAG.

No patient in this series suffered any untoward side effects from timolol eye drops.

Some graphs (Figs. 1–7) suggest that in some cases timolol may lose some of its effect—also a characteristic of many drugs, including pilocarpine and adrenaline. In studies on open-angle glaucoma only a slight loss of effect in the first few weeks of treatment has been observed.^{5 7 10 23 24}

Gonioscopic findings were not always consistent with tonometry. Sometimes it was difficult to be sure that posterior trabecular synechiae were absent in parts of the angle apparently open. Sometimes it was suspected that, although areas of angle were open, the meshwork was in fact occluded by im-

pacted peripheral iris (especially when pigmented) which had been left behind when iris bombé had collapsed, or when mechanical traction at (sector) iridectomy had failed to pull all layers of iris clear of the meshwork.

ADDENDUM. In a publication²⁵ received since this paper was written, namely, 'Timolol: its effectiveness in different types of glaucoma', Wilson *et al.* provide evidence in support of its title (including cases of chronic closed-angle glaucoma). Lass and Pavan-Langston²⁶ have also demonstrated its efficacy in closed-angle glaucoma following penetrating keratoplasty.

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Role of axoplasmic transport in the pathophysiology of ischaemic disc swelling

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SUMMARY Pathological changes in the optic disc and anterior part of the optic nerve of monkeys were studied 5 hours and several days after occlusion of the temporal short posterior ciliary arteries. Ischaemic vacuolation of neural tissue was observed in some of the animals studied and was restricted to the lamina cribrosa and the immediately retrolaminar portion of the optic nerve. Axonal swelling and organelle aggregation were demonstrated in the prelaminar region, and autoradiography after intravitreal injection of tritiated leucine revealed an associated obstruction of rapid and slow orthograde axoplasmic transport. The experimental findings correlate with those seen clinically in acute ischaemic optic neuropathy. The pale swelling of the optic disc in this condition represents an accumulation of axoplasmic debris in retinal ganglion-cell axons owing to obstruction of axoplasmic transport at the lamina cribrosa; it is thus equivalent to a 'cotton-wool spot' of the disc.

Acute ischaemic optic neuropathy (ION), characterised by sudden visual loss and pale disc swelling, results from obstruction of the blood supply to the anterior part of the optic nerve.¹⁻³ This is confirmed by necropsy studies in patients with ION, which show occlusion of the lumen of the posterior ciliary arteries (PCAs) and also necrosis of the most anterior part of the retrolaminar myelinated optic nerve.⁴⁻¹⁰ However, these studies have failed to clarify the nature of the ophthalmoscopically visible *prelaminar* swelling in ION. This sign was previously interpreted as an infarct of the disc,^{3,11} but more recently the prelaminar swelling has been attributed to an accumulation of opaque axoplasmic debris in the optic nerve head rather than infarction.^{12,13} In an attempt to resolve this issue, and since the immediate sequelae of experimental PCA occlusion have received scant attention in the past, we have reinvestigated acute ischaemic disc swelling in primates.

Material and methods

Cynomolgus and rhesus monkeys were used in these experiments, since their ocular vascular anatomy corresponds reasonably well with that of man.

Lateral orbitotomies were performed in order to

expose the temporal aspect of the optic nerve in 11 animals; the lateral rectus and inferior oblique muscles were routinely severed. All the short PCAs visible on the temporal, superior, and inferior aspects of the optic nerve were divided after coagulation by bipolar diathermy together with small vessels on the sclera around the insertion of the optic nerve. Care was taken to avoid damage to the dural sheath of the optic nerve and the underlying pial vasculature. In all experiments the short PCAs on the medial aspect of the optic nerve were spared so that 'control' data could be obtained. This was important, since the eye usually became hypotonic after orbitotomy and vascular occlusion. Occlusion of only the most accessible short PCAs also minimised mechanically induced changes in the optic nerve. Control data were also obtained by carrying out lateral orbitotomy and orbital dissection (but no vascular occlusion) in 5 eyes.

Fluorescein fundus angiography was performed within 1 hour of ciliary occlusion in all animals; 10% fluorescein solution was injected into a leg vein. The photographic methods have been described in a previous publication.¹⁴

0.25 ml of L-4, 5 ³H-leucine (specific activity 40-60 000 m Ci/mmol, Radio Chemical Centre, Amersham) was injected into the posterior vitreous after ocular massage via a 27 gauge needle inserted through the temporal pars plana. The injection was made over the optic disc and was continuously

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Table 1 *Details of 11 eyes undergoing temporal short PCA occlusion*

Number	Type	Eye	Duration of occlusion	Preocclusion ³ H-leucine	Retrolaminar infarct	Figure
1	Cynomolgus	Right	5 hours	$\frac{1}{2}$ h	+	4, 5, 7b
2	Cynomolgus	Left	5 hours	48 h	—	3
3	Rhesus	Left	5 hours	$\frac{1}{2}$ h	—	
4	Rhesus	Left	5 hours	$\frac{1}{2}$ h	—	
5	Rhesus	Right	5 hours	$\frac{1}{2}$ h	+	6, 7a
6	Cynomolgus	Left	4 days	48 h	±	2
7	Cynomolgus	Right	4 days	48 h	—	
8	Rhesus	Left	4 days	$\frac{1}{2}$ h	+	1, 9a
9	Cynomolgus	Right	4 days	$\frac{1}{2}$ h	—	
10	Rhesus	Right	4 days	$\frac{1}{2}$ h	—	
11	Cynomolgus	Left	7 days	$\frac{1}{2}$ h	+	9b

monitored by indirect ophthalmoscopy, care being taken to ensure that central arterial perfusion was maintained at the termination of the injection. The ³H-leucine was injected immediately before the ciliary occlusion in 8 eyes, or 48 hours before the vascular occlusion in 3 eyes (Table 1).

In acute experiments (5 eyes) the ischaemic lesion was allowed to develop for 5 hours before enucleation of the eye. In chronic experiments the ischaemic lesion developed for either 4 days (in 5 eyes) or 7 days (in 1 eye) before enucleation. Colour photographs of the fundus and further fluorescein angiograms were obtained during the interim period.

The eyes, including as long a length as possible of the optic nerve, were removed at the termination of the experiments, and after transcorneal incision were immediately immersed in 100 ml of 2.5% glutaraldehyde buffered in 0.1 M sodium cacodylate with a final pH 7.4. The eyes were progressively dissected in this solution, and after 1 hour the discs and optic nerves were isolated and then hemisected in the horizontal aspect. Thus during subsequent microscopy both temporal and nasal retina could be viewed simultaneously. In some eyes, where either an inferior or superior sectorial defect was suspected, the relevant half of the disc was quartered by an incision along the axis of the retinal nerve fibres. Subsequent histological and autoradiographic processing has been previously described.¹⁵

Results

FUNDUS CHANGES AFTER PCA OCCLUSION

Apart from slight hyperaemia there were no dis-

cernible changes in the ophthalmoscopic appearance of the optic disc and retina during the first few hours following occlusion of the temporal short PCAs. In the chronic experiments swelling of the optic nerve head was observed in 2 animals, the inferotemporal part of the disc being particularly involved (Fig. 1). Outer retinal infarcts were observed in all eyes in chronic experiments, though there was great variation in the extent of these changes; in none was there involvement of the immediately peripapillary retina.

FLUORESCIN ANGIOGRAPHY AFTER PCA OCCLUSION

In all eyes nonfilling of the temporal choroid in the early part of the central arterial transit confirmed the vascular obstruction (Fig. 2a). The choriocapillaris filling from the nasal short PCAs was contiguous with the adjacent margin of the optic disc and was initially sharply demarcated. Subsequently, however, the extent of choriocapillaris filling with fluorescein increased (Fig. 2b) and eventually included an area at least 1 disc diameter in width around the temporal aspect of the optic disc. Thus in all animals the immediately peripapillary choriocapillaris was completely filled by the late venous phase of the dye transit, and in some animals much more extensive filling of the temporal choroid was demonstrated.

Changes in fluorescein filling of the optic disc after PCA occlusion were generally more difficult to define because the central arterial supply to the superficial disc tissue obscured the filling pattern deeper in the optic nerve head after 2 or 3 frames. In 3 eyes, however, there was unequivocal filling

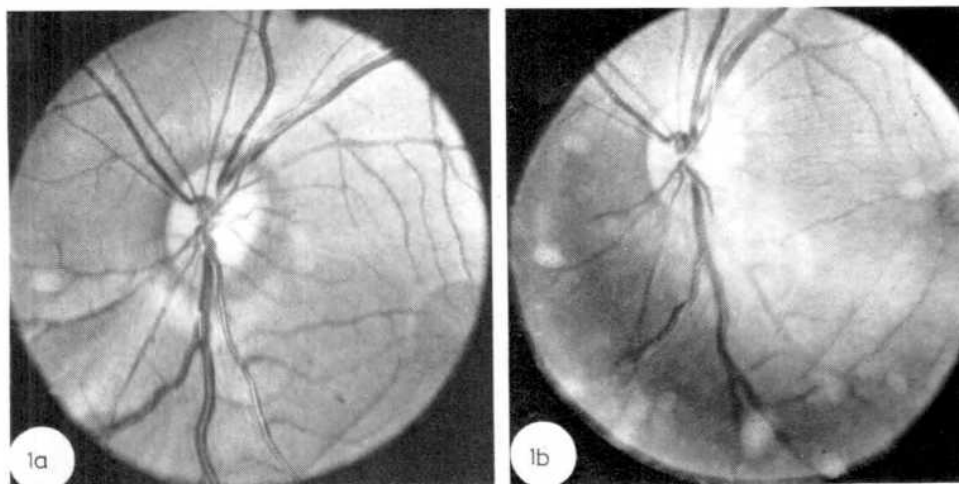


Fig. 1 Photographs of left optic disc of rhesus monkey: (a) Preoperative appearance. (b) Appearance 4 days after temporal short PCA occlusion; swelling of temporal half of disc, particularly inferotemporal quadrant

of the nasal part of the disc contiguous with the filled choriocapillaris at a stage early in the dye transit in which the temporal half of the disc could be seen to be nonperfused (Fig. 2a). This reversed the pattern of fluorescein filling in control fluorescein angiograms taken before vascular occlusion.

ACUTE HISTOPATHOLOGY

Light microscopy

The histological findings 5 hours after PCA occlusion showed considerable variation. In 3 eyes there

were no visible changes in the prelaminar, laminar, or retrolaminar portions of the nerve (Fig. 3), while in 2 others changes were apparent (Table 1). In neither group, however, was there any gross distortion of the topography of the disc or any apparent involvement of the peripapillary retina.

As retinal ganglion-cell axons pass back through the retinal layers at the disc, some exhibit a slight increase in diameter, so it may be difficult to discriminate between such normal expansions and any that may have been induced by experimental

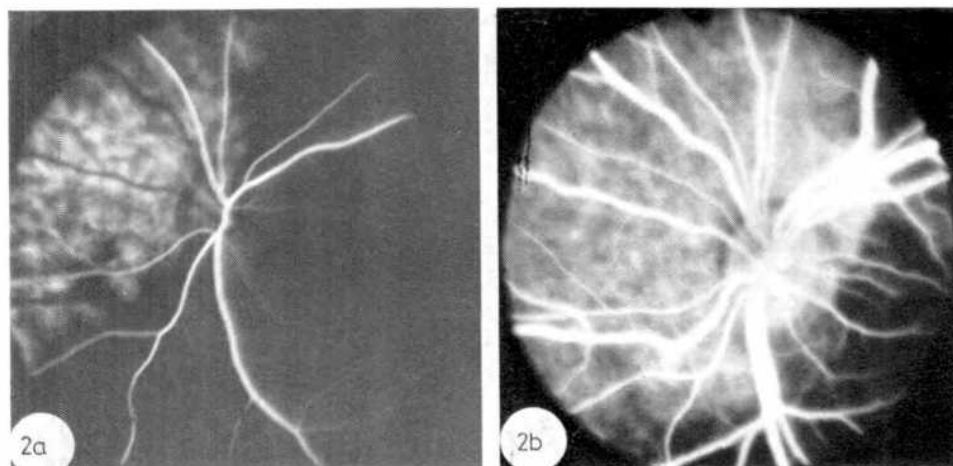
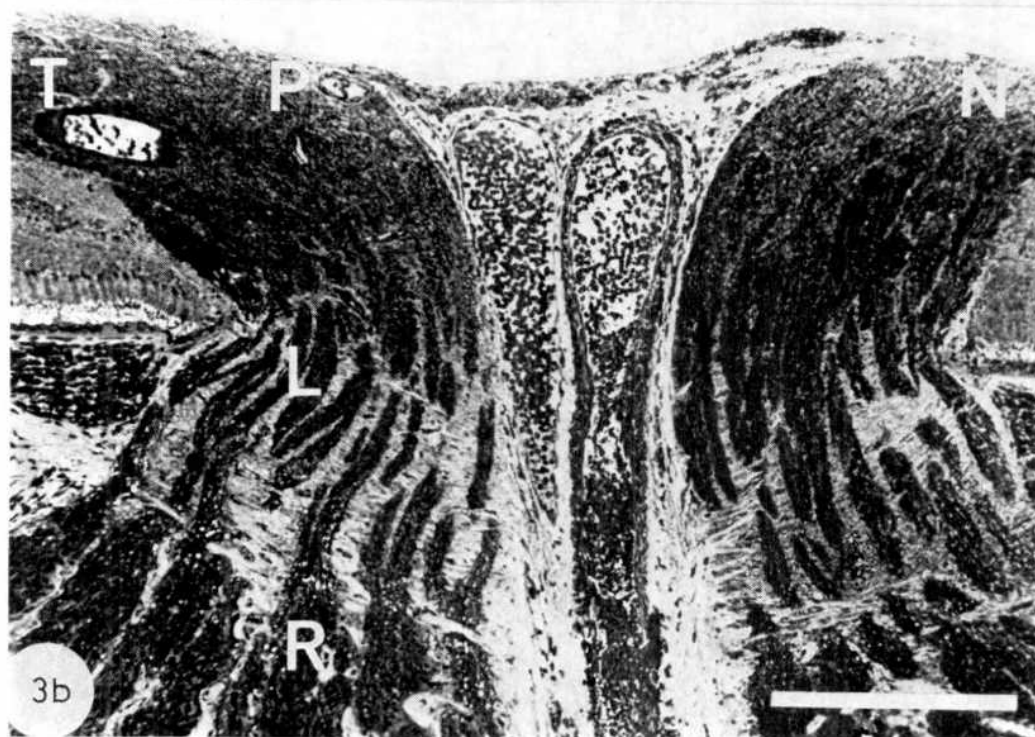
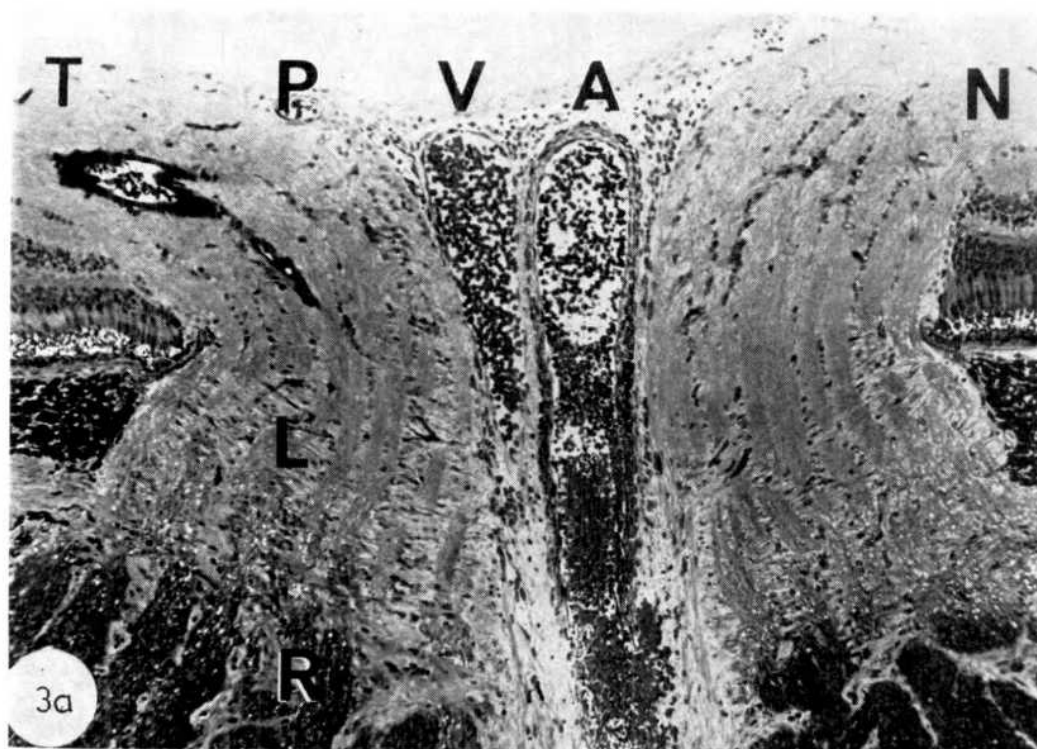


Fig. 2 Fluorescein angiograms 1 hour after temporal short PCA occlusion: (a) Early retinal arterial phase; nasal choriocapillaris and prelaminar circulation filling with dye; no filling of temporal choroid and disc. (b) Retinal venous phase; extension of filling of choriocapillaris into temporal peripapillary region.



procedures. In the 2 eyes showing damage there was an increase in both the diameter and staining density of many of the axons on the temporal side of the disc. In these animals, however, changes were most marked in the laminar and retrolaminar regions and in both cases were confined to the temporal half of the nerve (Fig. 4). Within the lamina many axons became progressively more vacuolated as they approached the retrolaminar portion of the nerve, but in both eyes some normal-looking axons were found. The glial elements in the lamina appeared relatively unaffected but occasionally showed slight irregularities in staining.

In the retrolaminar portion of the affected nerves, the myelinated axons on the temporal side were grossly vacuolated (Fig. 4a, b). At the periphery of this part of the nerve, however, many normal-looking axons were observed adjacent to the pia. In contrast, at the centre of the nerves there was an abrupt transition between normal and damaged axons. The axial extent of the vacuolated part of the nerve varied from $1\frac{1}{2}$ to 4 mm, and the posterior margin of damage consisted of a region of diffuse and dissociated vacuoles which gradually became less numerous.

Electron microscopy

In the unmyelinated prelaminar region individual axons normally contain large numbers of small mitochondria. In eyes showing damage an increase in mitochondrial numbers was noted as fibres approached the lamina on the temporal side. These mitochondria were smaller than normal, and many were electron-dense and looked degenerate. In association with these mitochondrial aggregates were many membrane-bound vesicles. Glial cells in the prelaminar region appeared unaffected by the experimental procedure.

As the fibres traversed the lamina, the mitochondria became progressively more degenerate, forming either condensed aggregates adjacent to the boundary membranes of the axons, or swollen

and vacuolated masses at the core of the axon surrounded by vesicles. Towards the retrolaminar region the microvacuolations within axonal organelles became confluent and began to disrupt the entire axonal cytoplasm (Fig. 5). Some glial cells within the lamina also showed microvacuolation.

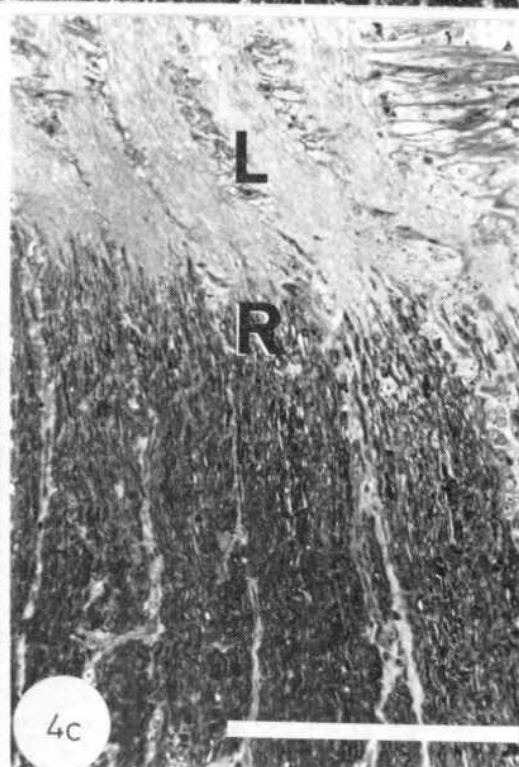
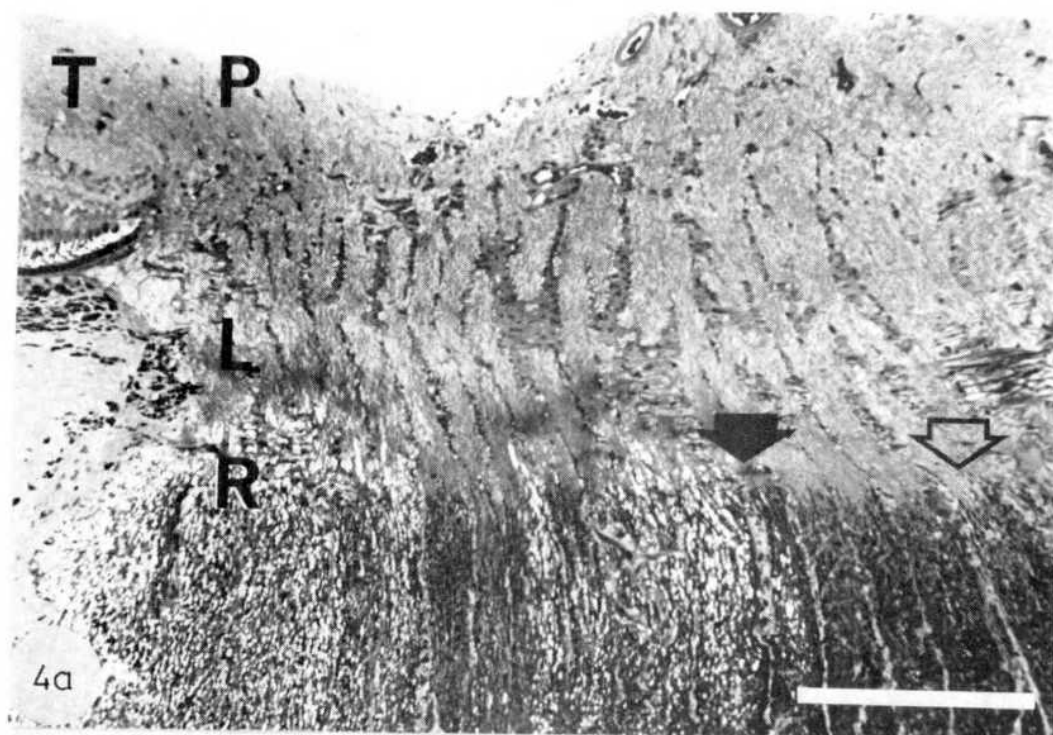
In the vacuolated retrolaminar region the cytoplasmic contents of the axons had been lost. Thus affected fibres appeared as well-preserved but distended myelin sheaths surrounding amorphous granular cytoplasmic debris in which occasional disrupted mitochondria were observed. As seen in the light micrographs, the distal edge of this region was diffuse, and no significant changes were observed in the axons where they returned to a more normal configuration.

Autoradiography

In unaffected and control nerves those portions of the disc receiving axons from the nasal retina were associated with a higher concentration of grains than those receiving inputs from the temporal fields (Fig. 3b). This observation may appear contrary to expectation given the high concentration of ganglion cells in the macula (Fig. 6). However, it was a consistent finding and possibly reflects differences in the speeds of rapid cellulifugal axonal flow on the nasal compared with the temporal side. It might also result from a greater labelled contribution in axonal material in our experimental time period due to less competition in obtaining radio-labelled protein in the sparse population of ganglion cells on the nasal side. In addition there was a slight increase in grain density over the prelaminar axons immediately adjacent to the lamina in all discs examined. This suggests that the lamina is the site of a natural constraint to the flow of materials in retinal ganglion-cell axons.

In those eyes in which a successful lesion had been produced, an extremely dense and highly localised concentration of silver grains was found on the temporal side of the disc in the prelaminar region immediately adjacent to the lamina (Fig. 7). The grain density on the experimental side was far in excess of that either on the collateral side or in the same region in control tissue. With increasing distance anteriorly from the lamina there was a progressive decrease in grain density, but there was an abrupt loss of grains over the vacuolated regions of the lamina and retrolaminar region (Fig. 7). Some grains were found in the vacuolated regions, but these were always associated with the few normal-looking axons. On the experimental side of the nerve no grains were observed over involved axons distal to the vacuolated region. The autoradiographic findings are summarised in Fig. 8.

Fig. 3 *Light micrographs of nerve showing no damage 5 hours after temporal short PCA occlusion: (a) Anterior portion of nerve sectioned in the horizontal plane and showing both temporal (T) and nasal (N) retina; prelaminar (P), laminar (L), and retrolaminar (R) portions of nerve identified; also central retinal vein (V) and artery (A). (b) Autoradiograph of same specimen (tritiated leucine injected intravitreally 53 hours prior to enucleation); relatively greater density of grain over axons on nasal side of prelaminar portion of the nerve (P). (Designations as in Fig. 3a; bar marker is 300 μ m)*



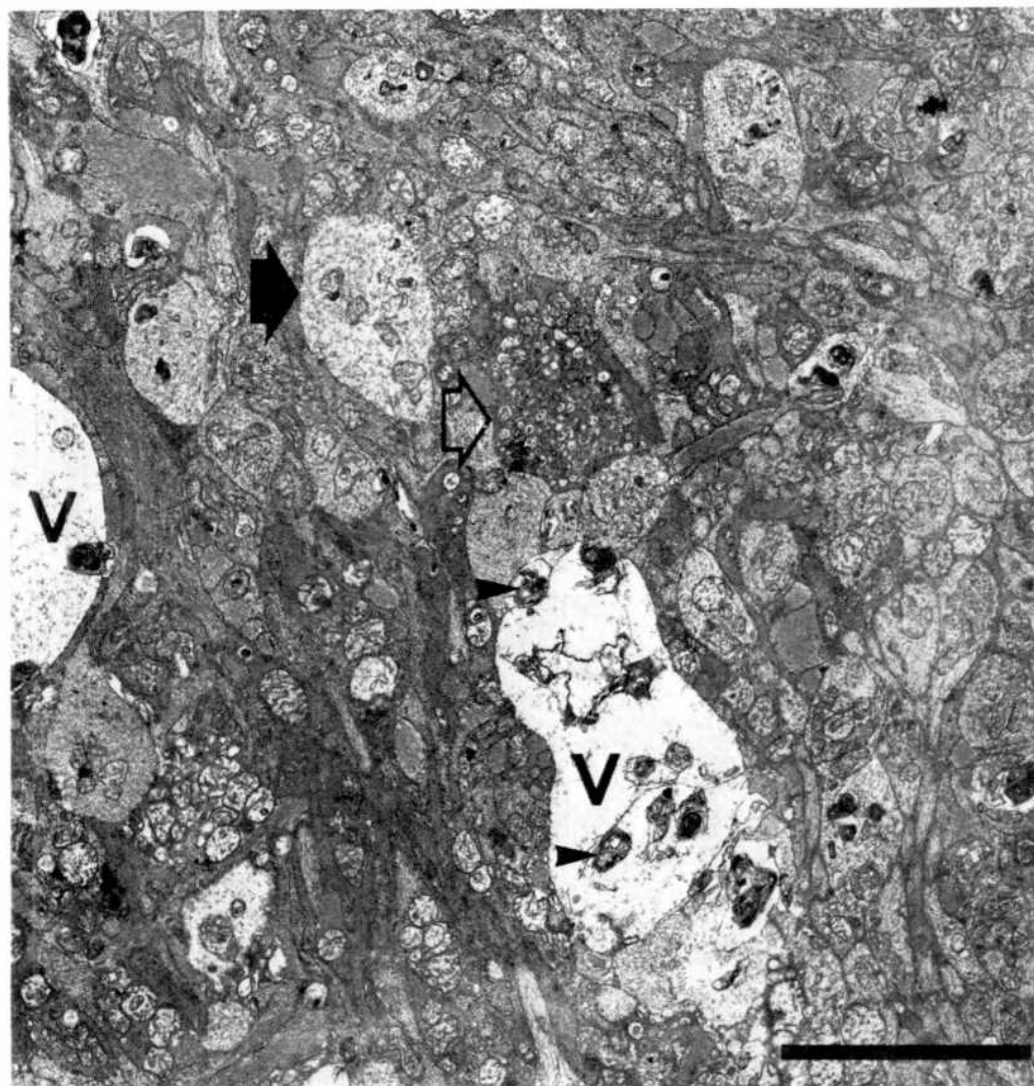


Fig. 5 Electron micrograph of laminar portion of nerve showing damage 5 hours after PCA occlusion. Vacuolation (V) and degenerate mitochondria (small arrows), together with both abnormally electron-dense (open arrow) and translucent (closed arrow) axonal swellings. (Bar marker is 4 μ m)

Fig. 4 Light micrographs of nerve showing damage 5 hours after temporal short PCA occlusion. (a) Vacuolated nerve fibres in retrolaminar portion of nerve on temporal side only (designations as in Fig. 3; bar marker is 300 μ m). (b) High-power view of vacuolated fibres from temporal retrolaminar nerve (solid arrow in Fig. 4a). (c) High power view of nasal fibres (open arrow in Fig. 4a; bar marker is 200 μ m)

CHRONIC HISTOPATHOLOGY

In 2 animals that survived for 4 and 7 days respectively after PCA occlusion and showed ischaemic damage (Table 1) both the microscopy and the autoradiography showed secondary changes which tended to obscure the focal distribution of the underlying pathogenic mechanisms.

In the prelaminar region swollen axonal stumps were observed some distance from the lamina, and on autoradiography these were identified as the sites at which orthograde axonal flow ceased (Fig.

9a). Separating these swellings from the lamina was an area of vacuolation which had presumably arisen as a result of retrograde degeneration of injured axons. Thus the accumulation of radio-active material in the prelaminar regions was more

diffuse in distribution, and more remote from the lamina, than in acute studies.

Secondary changes had begun to obscure the vacuolated areas in the laminar and immediate retrolaminar regions by the fourth postoperative

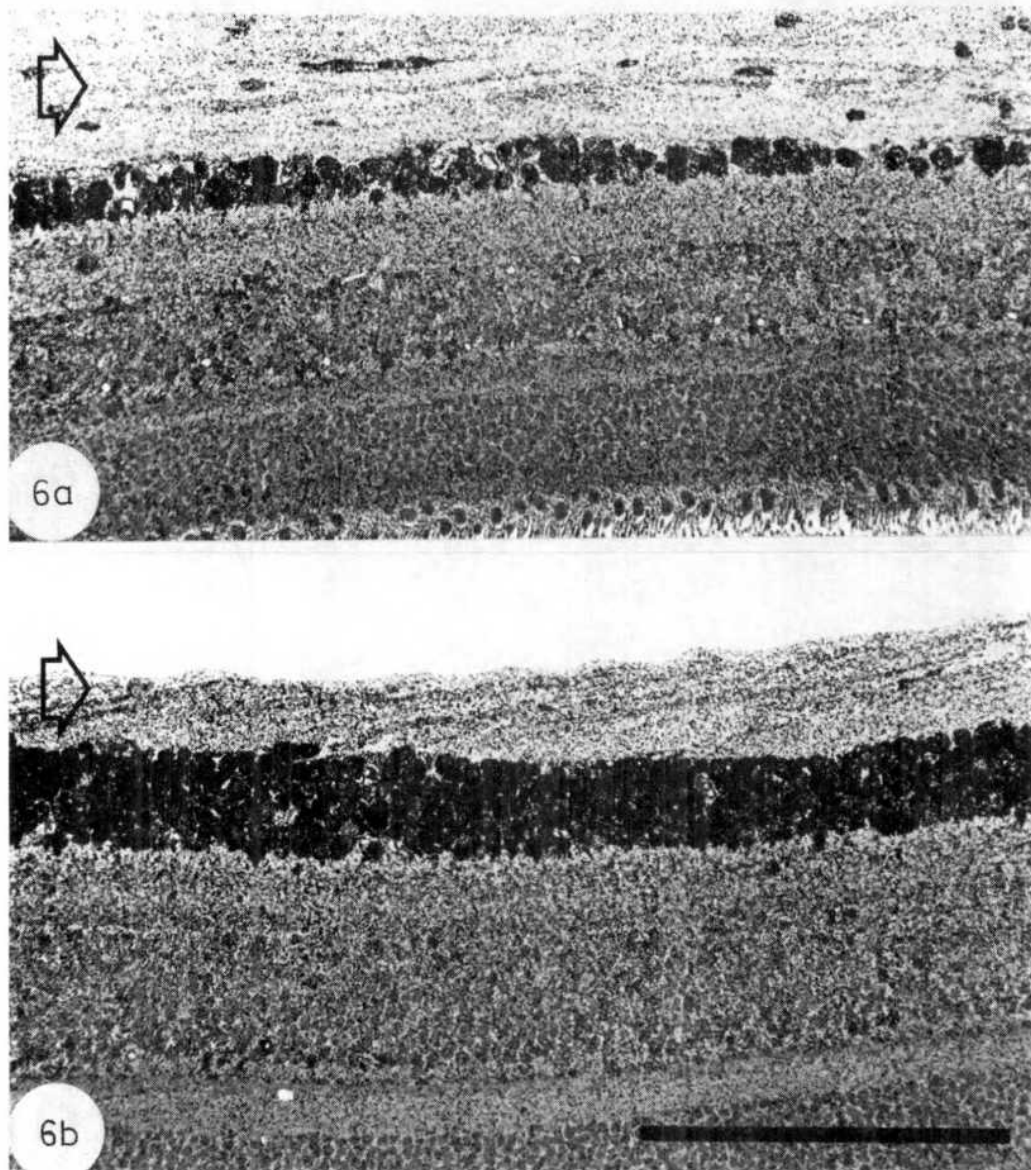


Fig. 6 Light microscopic autoradiographs of retina 5½ hours after intravitreal injection of tritiated leucine. Dense uptake of radiolabeled leucine into both ganglion-cell bodies and their axons (arrowed) from nasal (a) and temporal (b) areas of retina. (Bar marker is 200 μ m)

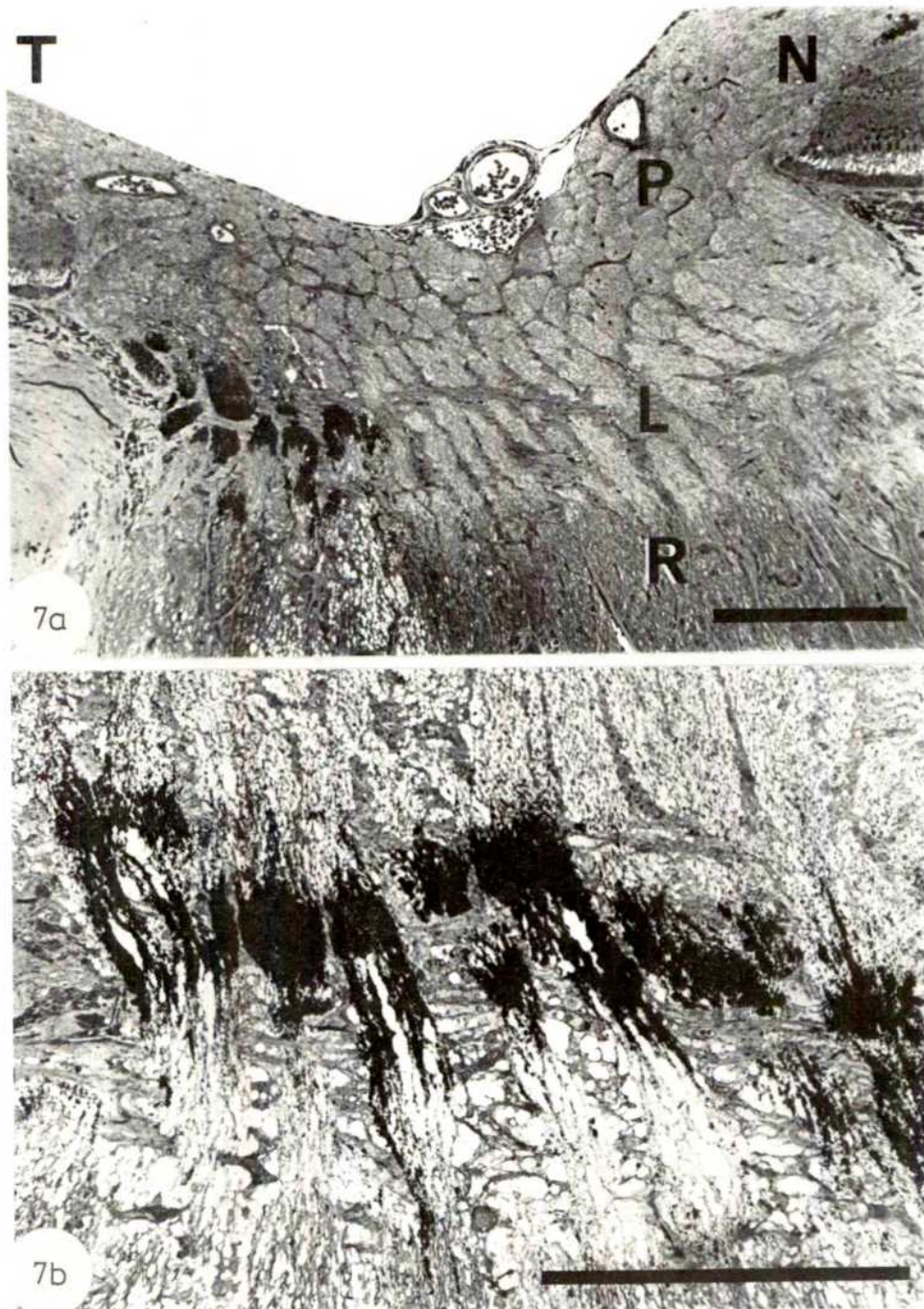


Fig. 7 Light microscopic autoradiographs of 2 nerves showing damage 5 hours after temporal short PCA occlusion and 5½ hours after intravitreal injection of tritiated leucine. (a) Accumulation of radioleucine in prelaminar and laminar portions of the nerve on temporal side (designations as in Fig. 3). (b) Higher power view of laminar portion of another nerve. (Bar markers are 200 μm)

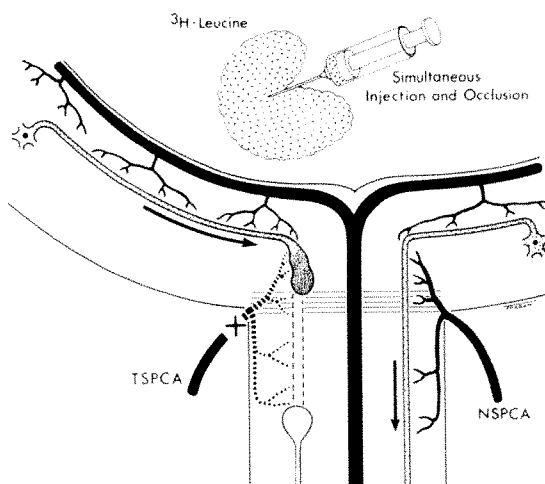


Fig. 8 Diagram of autoradiographic findings in retinal ganglion-cell axons after occlusion (X) of temporal short PCAs. Orthograde axoplasmic transport (arrows) obstructed in temporal prelaminar region adjacent to ischaemic vacuolation (axolemma dotted) in laminar and immediately retrolaminar regions. TSPCA = temporal short posterior ciliary arteries. NSPCA = nasal short posterior ciliary arteries.

day. After 7 days some of the myelin sheaths had begun to degenerate, and macrophages were found in the retrolaminar nerve (Fig. 9b). In both eyes many axons immediately adjacent to the pia on the temporal side had relatively normal morphology and showed normal axonal flow characteristics in the autoradiographs (Fig. 9a). However, some sections showed obstruction in the form of dense areas of grain over swollen regions some way into the retrolaminar nerve.

Posterior to the ischaemic area the zone of swollen axonal stumps isolated from their cell bodies was extremely diffuse and therefore difficult to identify. The individual swollen axon stumps were tapered, unlike the spheroidal swellings observed in unmyelinated portions of axons in an earlier report.¹⁵

Discussion

ARTERIAL SUPPLY TO THE ANTERIOR OPTIC NERVE

Apart from the superficial horizontal layer of nerve fibres both the optic disc and the immediately retrolaminar myelinated optic nerve obtain their blood supply from branches of the PCAs, which usually arise as 2 or 3 main trunks from the ophthalmic artery.³ Those short ciliary branches destined to supply the optic nerve head pass either directly

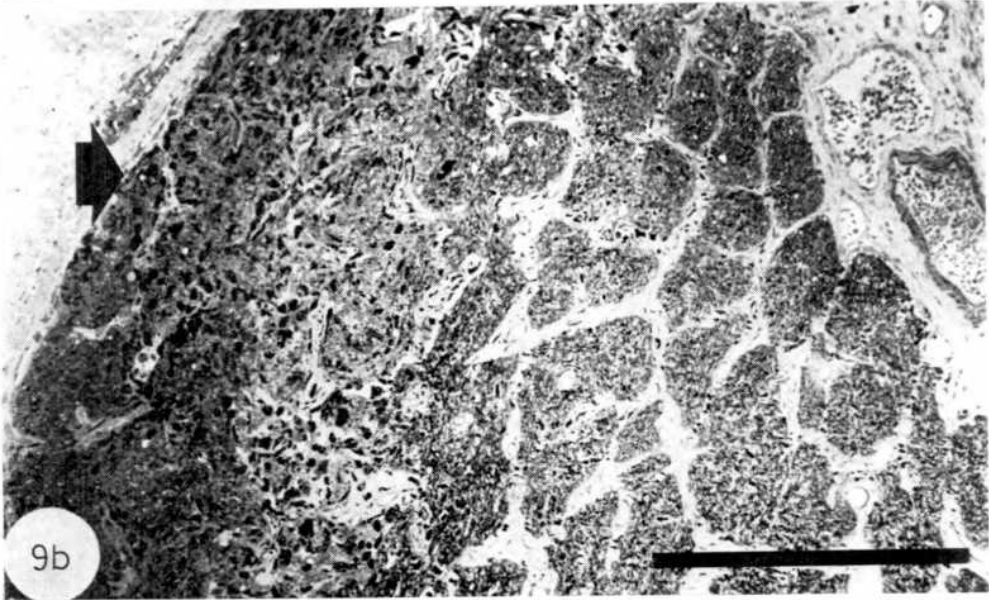
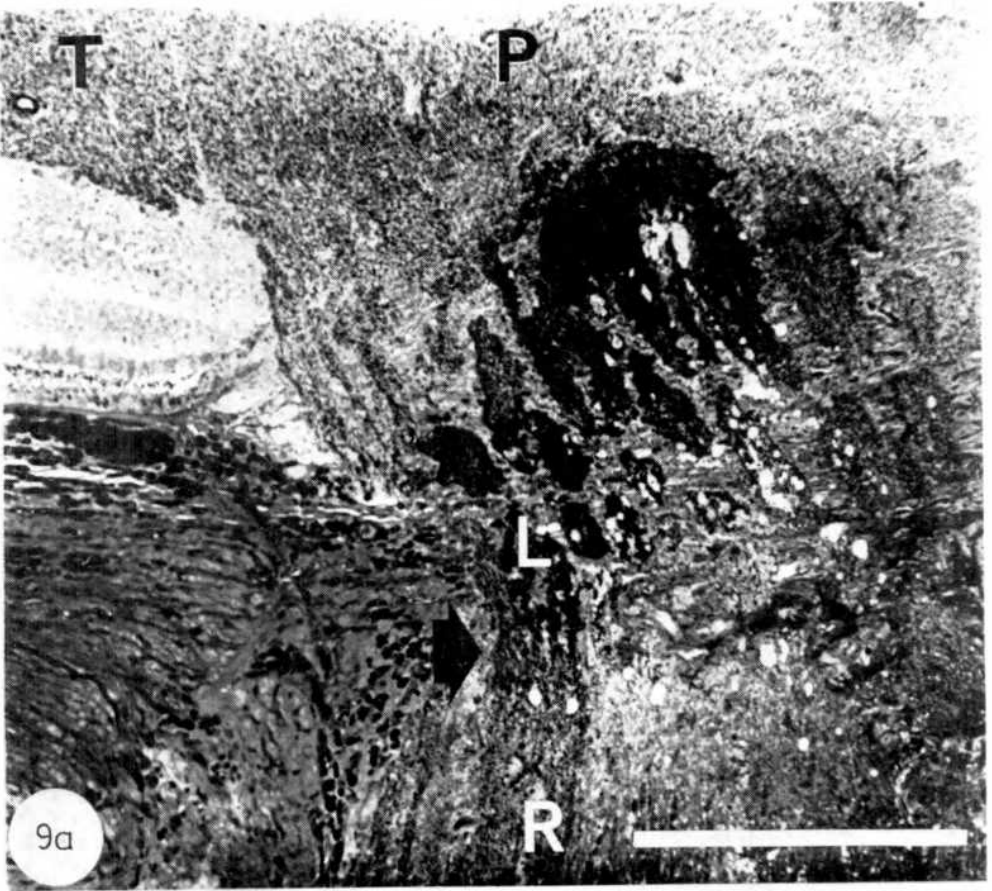
through the sclera or reach the disc indirectly via the peripapillary choroidal arteries; the latter route is more prominent in monkeys than in man.¹⁶ Posterior to the lamina cribrosa the optic nerve is mainly supplied by the pial plexus, which receives contributions from many orbital arteries, including the short PCAs and extraneural branches of the central retinal artery (CRA). In addition a relatively insignificant axial supply from branches of the intraneural CRA has been described in man.¹⁷ However, no intraneural branches of the CRA were found in various monkey species,^{18,19} and recent studies of blood flow using a heated thermocouple technique indicate that the short PCAs indeed provide the major vascular supply to the immediately retrolaminar part of the optic nerve in the rhesus monkey.²⁰

Each PCA normally supplies a defined territory with relatively little overlap in the area supplied.¹⁷ This 'segmental distribution' has been clearly demonstrated in the peripapillary choroid after intracarotid fluorescein injection in monkeys²¹ and in the initial frames of intravenous fluorescein angiograms after occlusion of several short PCAs, as in this study. Such experiments also indicate that the transversely orientated ciliary circulation to the lamina cribrosa may be sectoral. However, the prelaminar and retrolaminar vascularity also has a prominent anteroposterior orientation and continuity in addition to the transverse sectoral pattern emphasised by Hayreh.¹⁶

It has been claimed that each PCA acts functionally as an 'end-artery'²²—that is, as an independent arteriolar-capillary unit with no available inter-arterial or other precapillary anastomoses. After PCA occlusion necrosis would therefore be expected throughout the vascular territory, any capillary connections being insufficient to maintain tissue viability. There is, however, abundant anatomical evidence of arteriolar anastomoses both between individual branches of the PCAs, for example, an

Fig. 9 Light micrographs of nerve showing damage several days after temporal short PCA occlusion.

(a) Autoradiograph of nerve 4 days after PCA occlusion and intravitreal injection of tritiated leucine; section through inferotemporal quadrant of optic nerve head. Accumulation of radioactive material retracted away from lamina cribrosa into prelaminar region; flow of label into retrolaminar portion of nerve in axons adjacent to pia (arrowed). (Designations as in Fig. 3; bar marker is 300 μ m). (b) Light micrograph of retrolaminar portion of nerve 7 days after PCA occlusion; macrophages (arrowed) in damaged temporal portion of nerve. (Bar marker is 500 μ m)



incomplete intrascleral arterial circle of Zinn and an arterio-arteriolar network in the peripapillary choroid,²³ and also between the PCAs and adjacent arterial circulations, for example, via the posterior episcleral plexus and the pial plexus.²² That these anastomoses are indeed 'functional' after PCA occlusion is demonstrated by the fact that ischaemic damage is restricted to triangular patches of outer retina and in only a proportion of animals to sectors of the optic nerve. The various individual routes of collateral arterial supply after PCA occlusion have been demonstrated by latex and silicone rubber injection studies.^{22,24} These pathways may underlie the delayed filling of the temporal peripapillary choroid consistently found in our study in the late venous phase of fluorescein angiograms performed less than an hour after temporal short PCA occlusion. This pattern has also been described by Ernest and others,²⁵ though delayed filling of the temporal choriocapillaris was noted in only a minority of the animals studied by Hayreh and Baines.²²

In those eyes with optic nerve damage after PCA occlusion ischaemic vasculature was found only in the laminar and retrolaminar regions early after occlusion. This anteroposterior localisation of infarction had not been apparent from previous histological studies in which optic nerve changes were assessed several weeks after PCA occlusion. Hayreh and Baines²⁶ merely assumed that the ischaemic zone had included the prelaminar region in addition to the retrolaminar myelinated optic nerve, while Anderson and Davis²⁷ supposed that infarction of the optic disc was the cause of the ascending neuronal degeneration seen in the orbital part of the optic nerve. An explanation for the absence of ischaemic damage anterior to the lamina cribrosa 5 hours after PCA occlusion is not readily forthcoming, since prelaminar infarction might have been anticipated from the known distribution of the PCA supply.¹⁷ The preservation of neuronal viability anterior to the lamina cribrosa must reflect the effectiveness of collateral arterial connections (rather than provision of nutrients from other sources such as the vitreous). Anastomosis with the CRA circulation is the likeliest source of collateral supply, though this was virtually impossible to assess by fluorescein angiography in our experiments and was not apparent to Hayreh and Baines²⁶ in their silicone rubber injection studies. However, the demonstration of cilioretinal anastomosis after CRA occlusion²⁸ is in keeping with this suggestion.

The anteroposterior extent of retrolaminar infarction was variable, but was of a similar dimension to the zone of nonfilling by silicone rubber noted by

Hayreh and Baines.²⁶ The extent of necrosis also correlated with the reduction in tissue PO_2 noted in the optic nerve 3–4 mm behind the eye by Armaly and Araki²⁹ after short PCA occlusion.

NATURE OF ISCHAEMIC DISC SWELLING

Those eyes showing ischaemic damage after PCA occlusion had prelaminar changes of a fundamentally different nature from the infarct of the retrolaminar myelinated optic nerve. The unmyelinated ganglion-cell axons became swollen with neurofilaments and organelles but were not disrupted. Autoradiographic studies demonstrated an associated obstruction of orthograde axoplasmic transport and also confirmed that the boundary between viable and ischaemic axon segments after PCA occlusion was situated at the lamina cribrosa (and not more superficially). In acute lesions (i.e., after 5 hours) rapidly transported ^3H -leucine accumulated at the lamina cribrosa proximal to the retrolaminar infarct, while in survival experiments obstruction of slow axonal transport also contributed to the generalised accumulation of ^3H -leucine in the optic nerve head.

Levy³⁰ also described an obstruction of slow ^3H -leucine transport at the lamina cribrosa after PCA occlusion in rhesus monkeys. The relationship of this obstruction to changes in the retrolaminar myelinated optic nerve was not defined, however, and several other observations, for example, presence of macular oedema and subretinal haemorrhages, but absence of outer retinal damage, make Levy's findings difficult to interpret. A laminar obstruction of slow and rapid orthograde axoplasmic transport has also been described in papilloedema from raised intracranial pressure³⁰ and in ocular hypertension and hypotony.^{31,32} In these conditions, however, the continuity of ganglion-cell axons was not disrupted (at least in the initial stages), the axoplasmic transport block was incomplete, and mechanical rather than ischaemic obstruction of axoplasmic transport has been postulated.

Our histological and autoradiographic findings in the prelaminar region after PCA occlusion are similar to those in the retinal nerve-fibre layer adjacent to areas of experimental inner retinal ischaemia.¹⁶ Furthermore, the clinical appearance of the acutely swollen ischaemic disc is identical to that of the retinal cotton-wool spot. Ischaemic disc swelling and retinal cotton-wool spots both represent accumulations of axoplasmic debris adjacent to infarcts involving retinal ganglion-cell axons. This correlates with necropsy findings in patients dying within a few days of onset of visual loss from ION (Fig. 10). Kreibitz⁴ was the first to describe the pale retrolaminar infarct of the myelinated optic nerve

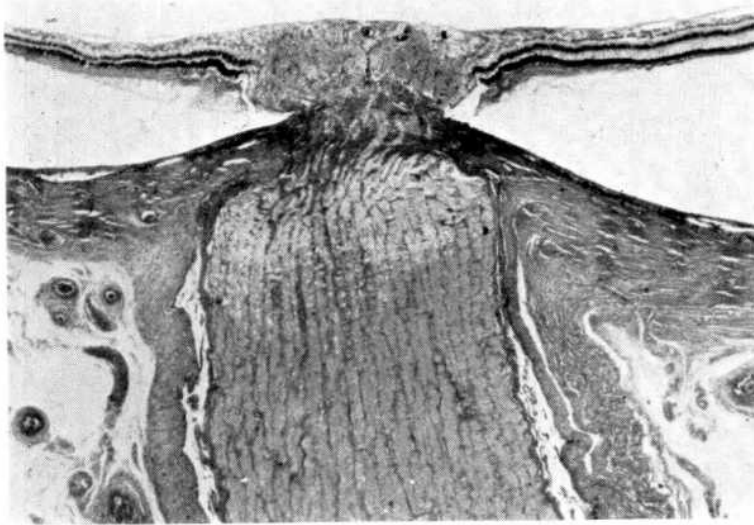


Fig. 10 Histopathology of human optic nerve 6 days after total visual loss from temporal arteritis. Retrolaminar infarction; prelaminar axonal swelling; arteritic occlusion of PCAs (courtesy of Professor Alec Garner).

in such cases while Rodenhauser⁷ noted 'cytoid bodies' (i.e., accumulations of axoplasm) in the prelaminar region.

The development of disc swelling after PCA occlusion depends on continuing orthograde axoplasmic transport in the nerve-fibre layer of the retina, so sufficient blood must continue to flow through branches of the CRA in order to maintain this transport function in the ganglion-cell axons. This is confirmed by clinical observation in cases of simultaneous combined CRA and PCA occlusion (where no opaque disc swelling develops). Similarly, in patients in whom ION is associated with occlusion of a large cilioretinal artery, no white swelling develops in the sector of the disc contiguous with the inner retinal infarct,¹³ so the translucent infarct of the inner retina and disc is continuous with that in the retrolaminar optic nerve.

It appears that the principal sign of ION, namely, pale disc swelling, can be entirely attributed to an accumulation of axoplasm in the prelaminar region. However, part of the disc swelling was recently attributed to infarction of the peripapillary pigment epithelium.^{11,17} This view was based on stereophotography of acutely ischaemic discs and the observation of pigmentary peripapillary degeneration at the stage of optic atrophy. It is significant, however, that identical pigmentary changes were present around the optic discs of the *unaffected* eyes in each of the cases presented by Hayreh in support of his contention. The absence of peripapillary pigment epithelial changes adjacent to ischaemic nerves after PCA occlusion in this study further denies the general concept proposed by Hayreh, though the authors are aware of rare authentic clinical examples

of peripapillary outer retinal infarction associated with ION.

SEGMENTAL ISCHAEMIC OPTIC NEUROPATHY

This concept is based on the transverse vascular architecture of the optic disc and signifies involvement of only a sector (rather than the whole) of the optic nerve head. Thus occlusion of part of the posterior ciliary supply (as in this study) may result in infarction within the territory of supply of the obstructed vessels, collateral circulation being insufficient to maintain tissue viability within the ischaemic area. There is no doubt that such cases occur in clinical practice (Fig. 11), although, unlike experimental PCA occlusion, ischaemic damage is usually confined to the optic nerve head (with no infarction of the outer retina). It has been suggested, however, that the typical visual field defect resulting from such an occlusion is a hemianopia whose vertical border passes through the blind spot, peripapillary choroidal ischaemia contributing to the field loss.^{17,21} We have been unable to confirm such a field defect clinically, however, and our autoradiographic studies of photoreceptor function after PCA occlusion fail to lend support to the concept that an absolute visual field defect would result from a degree of choroidal ischaemia insufficient to cause outer retinal infarction (Marshall, McLeod, and Kohner, in preparation).

Many patients with sectoral ischaemic optic neuropathy present with an inferior altitudinal hemianopia associated with pale swelling (and subsequent atrophy) of the superior half of the optic disc. Hayreh^{17,21} has repeatedly suggested that such an altitudinal hemianopia results from occlusion of

a main PCA supplying the upper half of the choroid and optic disc. However, this view has been justified only by the choroidal filling pattern seen after intra-carotid fluorescein injection in two monkeys which had previously undergone orbital dissection and

CRA occlusion.²¹ No such pattern of choroidal and disc filling has been seen in patients with altitudinal hemianopia, nor have anatomical studies revealed any horizontal division of the main PCA supply.²¹ Hayreh¹⁷ chose to illustrate the concept of a

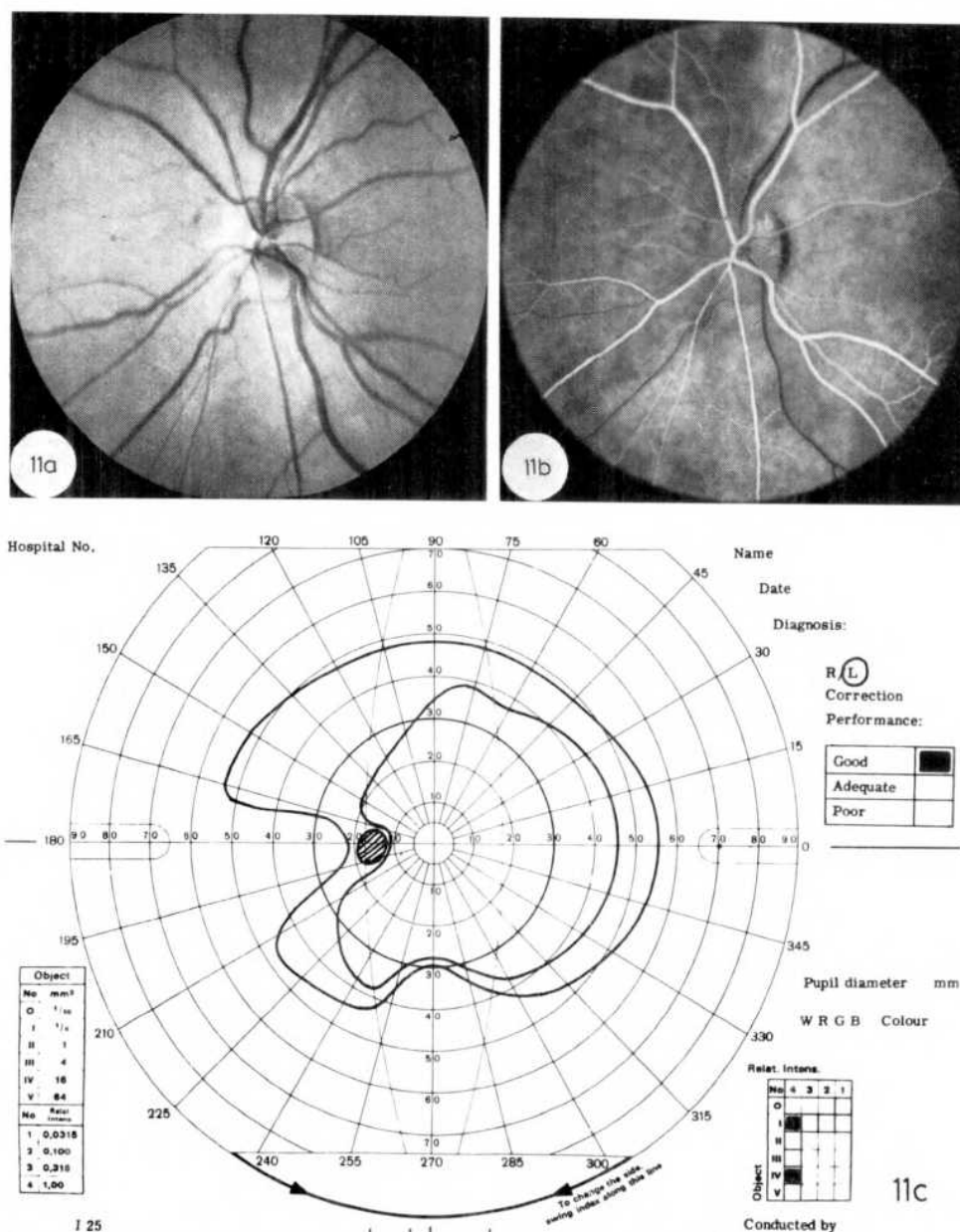


Fig. 11 Case of segmental ischaemic optic neuropathy. (a) Photograph of left optic disc; opaque swelling of prelaminar tissue nasally. (b) Fluorescein angiogram (arteriovenous phase); delayed filling of choriocapillaris in territory of medial PCA. (c) Goldmann perimetry; nerve-fibre bundle defects (courtesy of Professor Alan Bird)

segmental ION with a patient in whom vision was totally lost from PCA occlusion but in whom no accumulation of axoplasm occurred in that half of the disc that was contiguous with a large cilioretinal infarct. The disc appearance, however, depended on the underlying nature of ischaemic disc swelling,¹³ and the use of the term 'segmental ION' in such a case seems unwarranted. Hayreh^{11, 17} has also described examples of so-called 'sectoral ION' contiguous with infarcts of inner retina supplied by cilioretinal arterioles. It is likely, however, that these were cases of pure cilioretinal artery occlusion and that the disc swelling represented an accumulation of axoplasm resulting from obstruction of retrograde axoplasmic transport. Such an opaque accumulation of axoplasm in the optic nerve head after cilioretinal artery occlusion (and also after hemisphere branch retinal artery occlusion and CRA occlusion) should not be designated 'ION' even though the disc swelling is of a fundamentally similar nature.

We are grateful to Messrs P. L. Ansell and P. West and Ms E. Clarke and M. Foster for technical assistance; to Messrs T. Tarrant, K. Sehmi, and T. Bandle for photographic assistance; and Miss P. Davies for secretarial assistance.

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Peripheral retinal haemorrhages with papilloedema

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SUMMARY Two cases are described with severe intracranial hypertension, papilloedema, and a hitherto unreported haemorrhagic peripheral retinopathy. The marked disc swelling in these patients has probably contributed to a venous occlusive element resulting in the haemorrhagic retinopathy.

Haemorrhages on the disc and in the peripapillary region remain one of the diagnostic features of papilloedema. In very severe cases haemorrhages may be seen more extensively, but it is exceptional to see them beyond the radius of the macular region.¹ However, the vascular retinopathies such as those associated with systemic hypertension, diabetes mellitus, and retinal vein occlusion characteristically display diffuse retinal changes.²

We report 2 cases of papilloedema with extensive peripheral retinal haemorrhages due to raised intracranial pressure alone. We are not aware of previous reports of such a picture.

Case reports

CASE 1

The patient was a 30-year-old multiparous Libyan woman. She complained of throbbing occipito-frontal headache for 3 years. Initially the pain was intermittent and frequently woke her at night. After 2 years the headache subsided during her tenth pregnancy, but recurred shortly after delivery of the child, some 6 months prior to referral. For 2 months she had noticed deterioration of vision in both eyes. This was initially gradual but then accelerated, leading to complete blindness a month before her admission. Her only other symptoms were mild bilateral tinnitus and transient rotational vertigo when the headache was severe. There was no vomiting, and menstruation was normal. She denied drug ingestion apart from aspirin. Her mother suffered from hypertension.

On examination she was grossly obese. Her blood pressure was 150/90 mmHg, and the heart, chest, and abdomen were clinically normal. There was no perception of light in either eye. The pupils were

equal at 4 mm and fixed. The optic discs were pale and swollen (Fig. 1), and there was a diffuse haemorrhagic retinopathy with numerous peripheral haemorrhages (Fig. 2). Intraocular pressure was normal, and ophthalmodynamometry showed pressures of 60/30 right and 60/20 left. Upward gaze was limited to 10 degrees; the eye movements were otherwise normal. There was a first-degree end point horizontal nystagmus to right and left. The remaining cranial nerves, including caloric responses, were normal. In the limbs there was no weakness, the reflexes were symmetrically sluggish, and the plantar responses were flexor. Sensation was normal. Her gait was slightly unsteady but not unduly so considering her blindness.

Investigations

Skull x-ray showed a thin and slightly eroded lamina dura of the dorsum sellae compatible with raised intracranial pressure. Computerised tomography showed normal ventricular size and position with no evidence of space occupation. Right carotid angiogram, vertebral angiogram, and lumbar air encephalogram were normal. An EEG was of low voltage with poorly developed alpha rhythm and no detectable responses to flicker. Lumbar puncture showed an opening pressure of 460 mm of water, rising to 500 mm on jugular compression. The CSF contained 114 red and 3 mononuclear cells $\times 10^6/l$ and protein 55 mg/100 ml (0.55 g/l); CSF Lange curve, IgG, sugar, Wassermann reaction, and cytology were normal. The ESR was recorded at 26 and 5 mm in 1 hour. The following investigations were normal: haemoglobin, PCV, white cell count and differential, platelet count, serum B_{12} and folate, blood urea, electrolytes, sugar, calcium, phosphate, liver function tests, protein electrophoresis, autoantibodies, urine analysis, chest x-ray, and electrocardiogram.

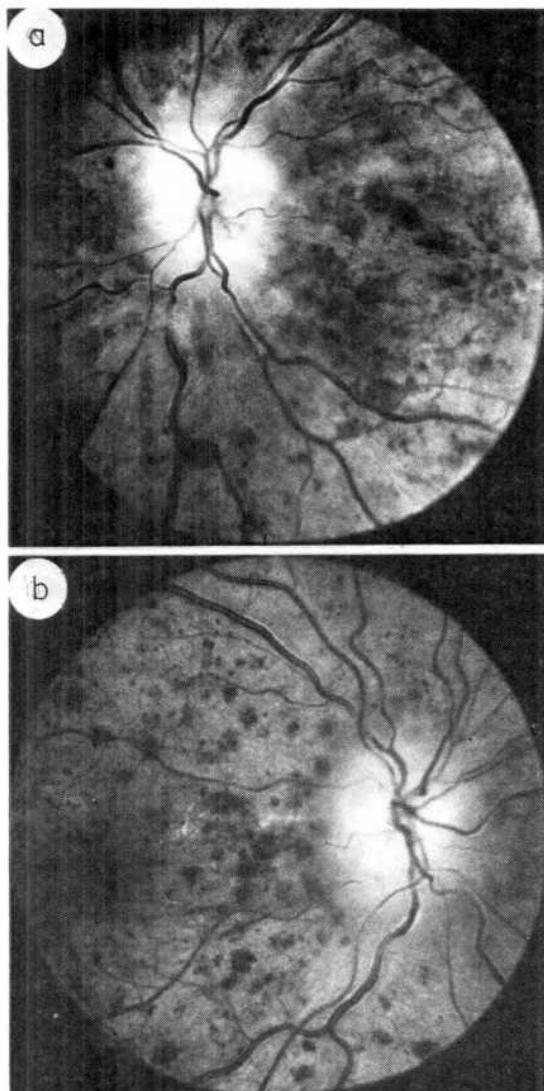


Fig. 1 (Case 1). Copy of colour photograph to show bilateral atrophic papilloedema with multiple punctate retinal haemorrhages in both eyes: a, right; b, left.

Management

After a short course of steroids her CSF pressure fell to 340 mm water. In view of the visual status, with little hope of recovery, and in the absence of any remediable lesion the steroids were discontinued.

CASE 2

This patient was a previously fit nulliparous housewife aged 21 years. She had been taking a low-oestrogen oral contraceptive for 6 months. Twelve

days before admission she had an upper respiratory tract infection that subsided in 48 hours. Two days later she noticed aching in both her shoulders, stiffness in her neck, and swelling of the second joint in her right hand. The following day she developed nausea and vomiting and became aware of frequent brief, jagged yellow flashes of light before both her eyes. She noticed intermittent double vision and that this was associated with her left eye turning inwards. She attended a general practitioner at this stage and migraine was diagnosed.

With simple analgesics her pains eased, but on the sixth day she developed intermittent tingling paraesthesiae in the face and hands. Over the next 48 hours she had recurrent episodes of giddiness, unsteadiness of gait, and a single brief period of loss of consciousness without convulsion and heralded by visual impairment. On the 11th day her vision deteriorated dramatically. Transient obscurations were followed by persisting upper field loss and finally a deterioration to perception of light bilaterally.

Examination showed her to be an obese young woman whose blood pressure was 140/80 mmHg. The heart and chest were normal and there were no abdominal masses. The visual fields were constricted to small central islands where acuity was reduced to counting fingers. There were frequent obscurations when she sat upright. She had gross bilateral papilloedema with infarcted discs and multiple peripapillary haemorrhages (Fig. 3). There were in

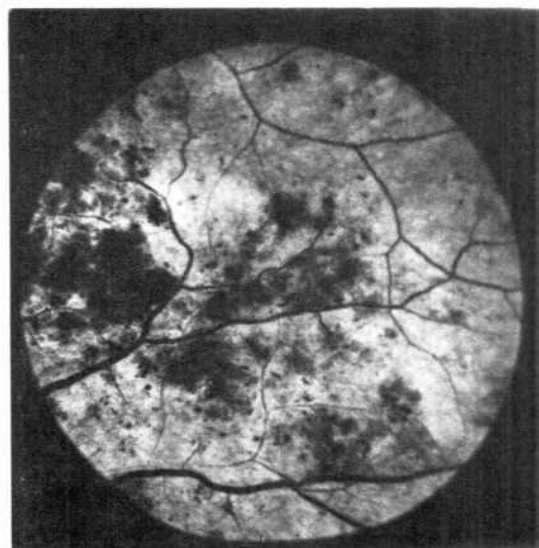


Fig. 2 (Case 1). Periphery of left eye to show punctate haemorrhages.

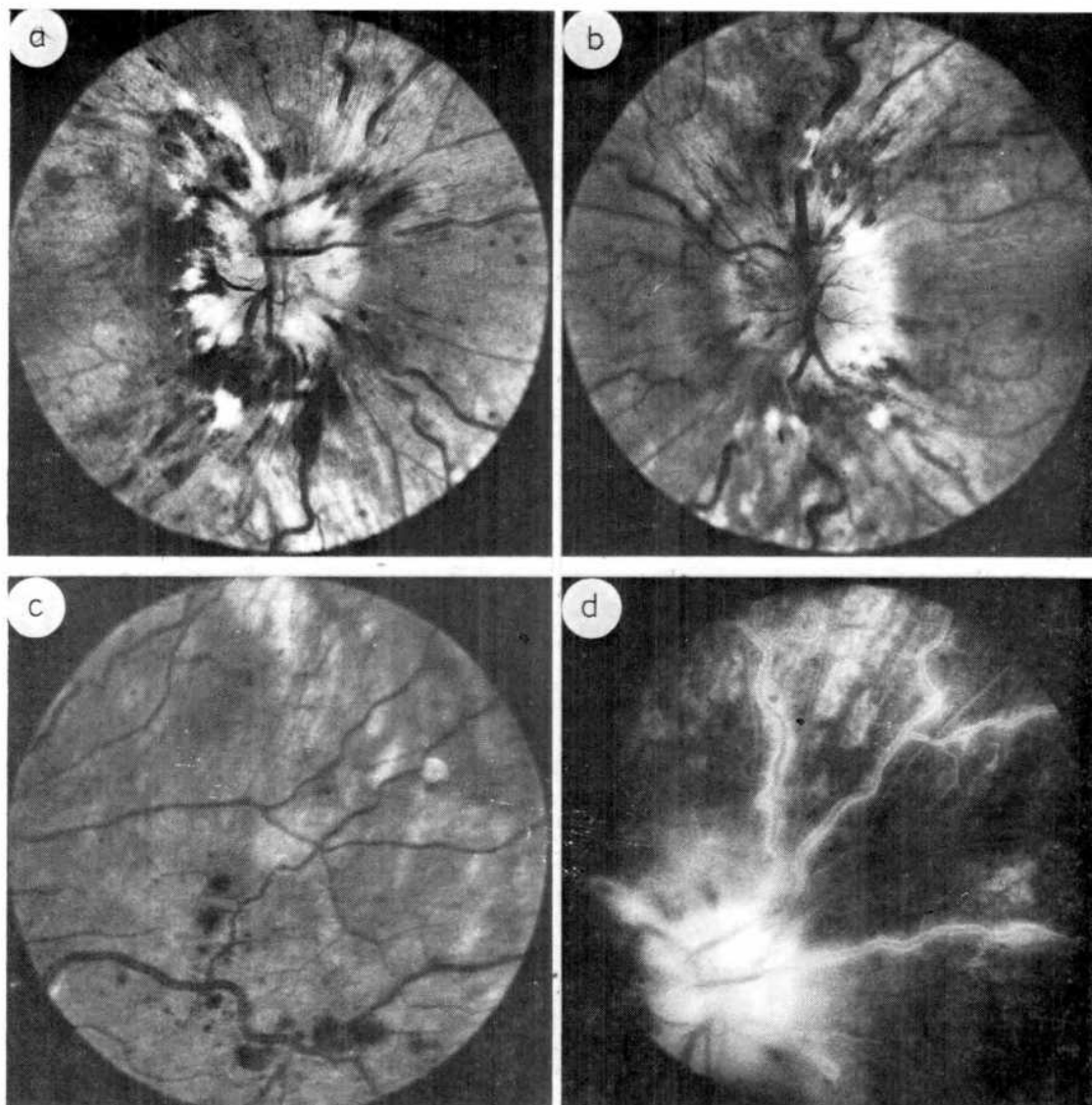


Fig. 3 (Case 2). Copy of colour photograph of both eyes to show disc swelling and peripapillary cotton-wool spots, with haemorrhages extending to the periphery: 3a, right; 3b, left.

Peripheral haemorrhages with a perivenous distribution in left eye (3c) and a late fluorescein angiogram of the right eye (3d) to show diffuse perivenous leakage of dye and residual disc leakage.

addition obvious peripheral haemorrhages in both fundi. These were associated with considerable venous leakage on fluorescein angiography. The pupils were widely dilated with a poor light response. She had a partial right sixth nerve weakness. The cranial nerves were otherwise normal. The reflexes, with the exception of ankle jerks, were absent and the plantar responses were bilaterally extensor.

There were no abnormal sensory or cerebellar signs.

Investigations

An EMI scan showed small ventricular size and no evidence of a space occupying lesion. Lumbar CSF pressure was in excess of 400 mm of water. The fluid was clear and contained 1 red and 3 mono-

nuclear cells, a protein of 18 mg/100 ml (0.18 g/l) and a normal sugar. The EEG showed a mild diffuse abnormality with a slowing of dominant rhythm to 7 c.p.s. and a moderate excess of theta activity. There was no focal lesion. Blood count showed a mildly elevated haemoglobin at 17G (PCV 49%: RBC 5.4×10^6). There was a polymorphonuclear leucocytosis. Platelet count was normal. The remaining investigations were normal. These included: ESR, sugar urea, electrolytes, osmolalities, Astrup test, calcium, phosphate, proteins, liver function, lead, autoantibodies, blood and CSF viral studies, Wassermann reaction, and culture of blood, stools and sputa, x-rays of chest, skull, and cervical spine, motor nerve conduction velocity, and sensory nerve action potentials.

Course and progress

The raised intracranial pressure was initially treated by repeated lumbar puncture, dexamethasone, acetazolamide, and glycerol. Her systemic symptoms resolved and her visual acuity improved to 6/6 right and 6/9 left, but still with marked field constriction and occasional postural obscurations. The retinal haemorrhages resolved and the discs developed marked optic atrophy. Despite the repeated lumbar punctures and drug therapy, her CSF opening pressure remained elevated at 300 mm of water. Because of this and increasingly Cushingoid features a thecoperitoneal shunt was inserted 10 weeks after her admission. Her CSF pressure settled to normal after this and remained so when steroid therapy was discontinued.

Discussion

In their classic paper Paton and Holmes¹ postulated that papilloedema was due to a rise in optic nerve sheath pressure producing compression of the intravaginal portion of the central retinal vein. They also attributed obstruction of lymph drainage from the papilla to an effect of the elevated sheath pressure. The haemorrhages were attributed to venous engorgement and the stretching and rupture of small disc capillaries.

For over a decade Hayreh^{2,4} has performed a series of experiments on rhesus monkeys and demonstrated that optic disc swelling is the first change in disc oedema in raised intracranial pressure. Elevated optic nerve sheath pressure causes a rise in optic nerve tissue pressure, stasis of axoplasmic flow,⁵ and swelling of the nerve fibres in the optic nerve head.⁶ This swelling then compromises the low pressure, predominantly venous, fine blood supply to the prelaminar region, and initiates a

vicious circle of oedema, congestion, and further oedema.⁷ The vascular changes on the nerve head are secondary to and not the cause of the disc oedema.⁷

Our cases show papilloedema in conjunction with peripheral retinal haemorrhages and a markedly elevated intracranial pressure. The clinical diagnosis in case one is 'benign' intracranial hypertension. Case 2 displays many of the features of this condition, but the diagnosis is not tenable in the context of a febrile illness, loss of tendon jerks, and extensor plantar responses, and remains one of raised intracranial pressure of uncertain aetiology.

The appearance of retinal haemorrhages varies according to their site in the retina, but the underlying mechanism remains identical with abnormal endothelial function due to anoxia. Anoxia at a capillary level can be readily understood in the small vessel disease of hypertension and diabetes mellitus. The combination of stasis, anoxia, and venous congestion in central retinal vein occlusion leads to profuse and characteristically peripheral retinal haemorrhage. Other stasis retinopathies behave similarly. The engorged veins, stasis, and superficial and deep haemorrhages of polycythaemia also occur with venous congestion and anoxia. In dysproteinaemia there is venous congestion and segmentation of blood flow, again conducive to anoxia, and fluorescein studies show circulatory delay and increased capillary permeability. There was no evidence of hyperviscosity or polycythaemia in either of these patients.

Paton and Holmes¹ demonstrated dilatation of the whole intraneural portion of the central retinal vein and also showed venous and capillary congestion in the retina, especially in the nerve fibre layer, for a short distance from the disc margin. It should be remembered that their pathological study was performed on the eyes of patients who had died from end stage, presumably very high, elevation of intracranial pressure. We feel that the marked elevation of pressure demonstrated in our patients led to a similar venous congestion and that, although this was not florid, it was enough to produce the retinopathy when acting together with the anoxic factor. The appearances we report are highly unusual, but recognition may be diagnostically important and alert the ophthalmologist to the occurrence of a haemorrhagic retinopathy with extreme elevation of intracranial hypertension.

We would like to thank Dr J. Morgan-Hughes and Dr R. Kocen for allowing us to use their cases.

We thank Mr Rolf Sennhenn for the photography and Mrs Gaye Jurewicz for secretarial assistance.

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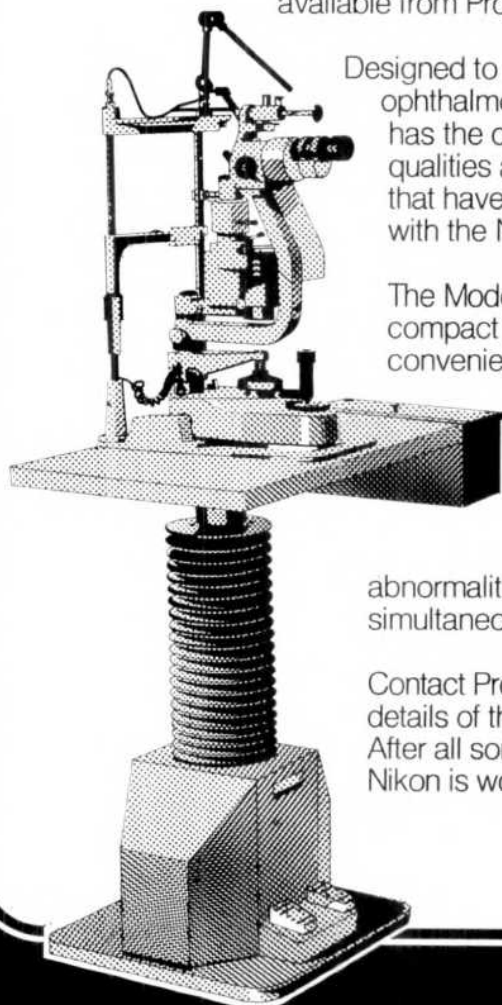
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Acquired optociliary shunt vessels in papilloedema

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SUMMARY Seven cases are presented in which prolonged papilloedema led to the development of acquired optociliary shunt vessels. These vessels may also be found with optic nerve tumours, particularly sphenoidal meningiomas, optic nerve drusen, glaucoma, and after central retinal vein occlusion. Two patients had intracranial tumours, 4 benign intracranial hypertension, and one Crouzon's disease. Three had marked atrophic changes of the disc. The pathophysiology of the disc changes is discussed. The triad of long-standing poor vision, acquired optociliary shunts, and optic atrophy with blurred disc margins should not be regarded as specific for sphenoidal meningioma.

Acquired optociliary shunt vessels present a rare and distinctive clinical appearance. There have been several reports of these vessels due to sphenoidal meningiomas.¹⁻³ These vessels have also been noted in association with optic nerve glioma,^{4,5} optic nerve arachnoid cyst,⁶ optic disc drusen,⁷ glaucoma,⁸⁻¹⁰ and after central retinal vein occlusion.¹¹⁻¹³ There are some early references to the occurrence of these shunt vessels in papilloedema¹⁴⁻¹⁶ but few modern documented cases.^{17,18} We therefore present 7 cases of optociliary shunt vessels occurring with papilloedema.

Patients and methods

CASE 1

A 37-year-old housewife was admitted for increasing weakness of the left arm and leg of 2 years duration and several recent attacks of focal epilepsy. Her past history included migraine episodes for the past 6 years. The general physical examination was unremarkable. Neurological examination showed left pyramidal tract signs and diminished 2-point discrimination in the left hand. There was a loud bruit audible all over the skull. The ocular examination showed a corrected visual acuity of 6/6, N6 in the right eye and 6/5, N5 in the left. There was a right relative afferent pupillary defect. Perimetry showed the visual field of the left eye to be full, but there was some constriction of the nasal field of the

right eye. The optic discs had blurred margins and were somewhat pale. The right was paler than the left. There were small drusen-like bodies at the disc margins and tortuous optociliary shunt vessels on both discs. Fluorescein angiography in both eyes showed mild dilatation of the radial peripapillary capillary plexus overlying the disc and nearby retina and leakage of dye into the surrounding retina, confirming the presence of papilloedema (Fig. 1). The shunt vessels filled from the retinal circulation. Arteriography demonstrated a massive superficial arteriovenous malformation in the right middle cerebral artery territory.

CASE 2

A 37-year-old electrician was evaluated for diminished visual acuity in the left eye of indeterminate duration and 3 months of intermittent visual obscurations of both eyes. The obscurations were consistently brought on by running down stairs or bending over. The general and neurological examinations were normal except for bilateral papilloedema. Corrected visual acuity was 6/6 in the right eye and 6/18 left. There was a left relative afferent pupillary defect. Perimetry showed the visual field of the right eye to be moderately constricted in a concentric pattern, and the visual field of the left eye to be markedly constricted, especially nasally. There was bilateral papilloedema with tortuous optociliary shunts and temporal pallor of the left disc (Fig. 2). Fluorescein angiography showed profuse dye leakage at both discs and demonstrated the shunt vessels in the left eye to fill from the retinal veins. At operation a colloid cyst of the third ventricle was removed.

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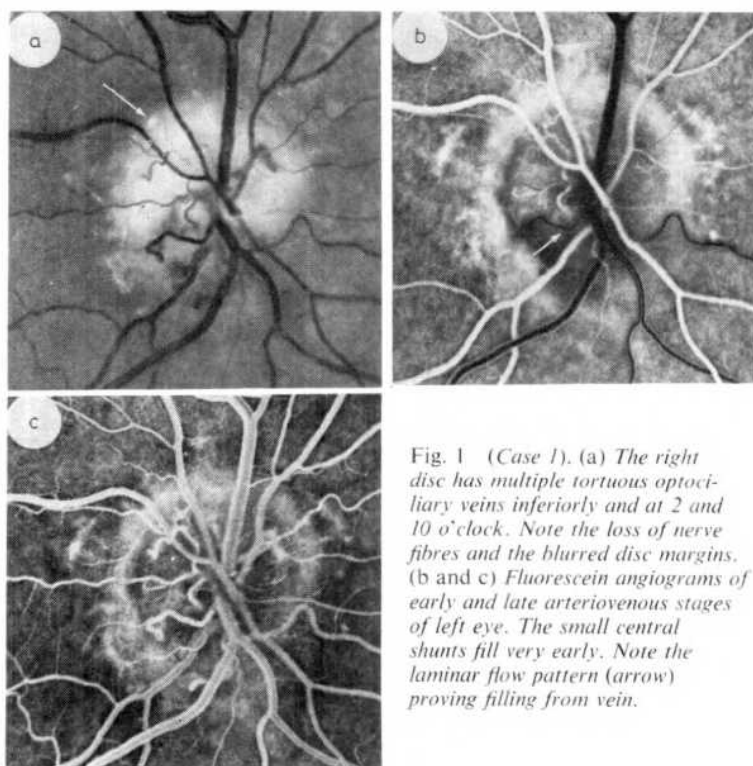


Fig. 1 (Case 1). (a) The right disc has multiple tortuous opticociliary veins inferiorly and at 2 and 10 o'clock. Note the loss of nerve fibres and the blurred disc margins. (b and c) Fluorescein angiograms of early and late arteriovenous stages of left eye. The small central shunts fill very early. Note the laminar flow pattern (arrow) proving filling from vein.

CASE 3

A 43-year-old executive presented with a 6-month history of progressive visual deterioration, predominantly of the left eye. The general and neurological examinations showed some blunting of the intellect, right sided hyposmia, and pathologically brisk reflexes of the left arm, but was otherwise unremarkable. The ocular examination showed a visual acuity of 6/5 in the right eye and counting fingers at 1 m in the left. There was a left relative afferent pupillary defect. Perimetry showed a right inferior temporal defect extending to the enlarged blind spot, but not the midline, and a small temporal island of vision remaining in the left eye. There was bilateral chronic papilloedema with moderate atrophy of the left disc, which had an ectatic, tortuous shunt vessel. Fluorescein angiography showed leakage at the discs and demonstrated the shunt vessel to fill from the retinal circulation. At surgery a right subfrontal meningioma was removed. Repeat examination 11 days postoperatively showed the shunt vessel to have disappeared (Fig. 3).

CASE 4

A slightly obese 20-year-old female was evaluated for headaches. General physical and neurological

examinations were normal. Visual acuity was 6/4.5, J1 in each eye. Pupillary light reflexes were normal. The blind spots were enlarged bilaterally, and there was a mild general depression of both visual fields. Bilateral papilloedema was present. Cerebrospinal fluid pressure was measured at 360 mm water. All laboratory and radiological studies, including computerised tomography, were normal. A diagnosis of benign intracranial hypertension was made. Fundus photography was performed 2 years later, at which time opticociliary shunt vessels were noted. At this time the cerebrospinal fluid pressure was measured at 250 mm water.

CASE 5

A 33-year-old male was evaluated for visual loss in the right eye of 2 years' duration. General physical and neurological examinations were normal. Visual acuity was no light perception in the right eye and 6/5, N5 in the left. The visual field of the left eye showed an inferior defect and constriction of all isoptres. There was bilateral papilloedema. The discs were pale, and opticociliary shunt vessels were present on the left. Radiological studies were normal, save for an enlarged sella. Computerised tomography showed the ventricles to be of normal size. The optic nerves were curved in the orbits

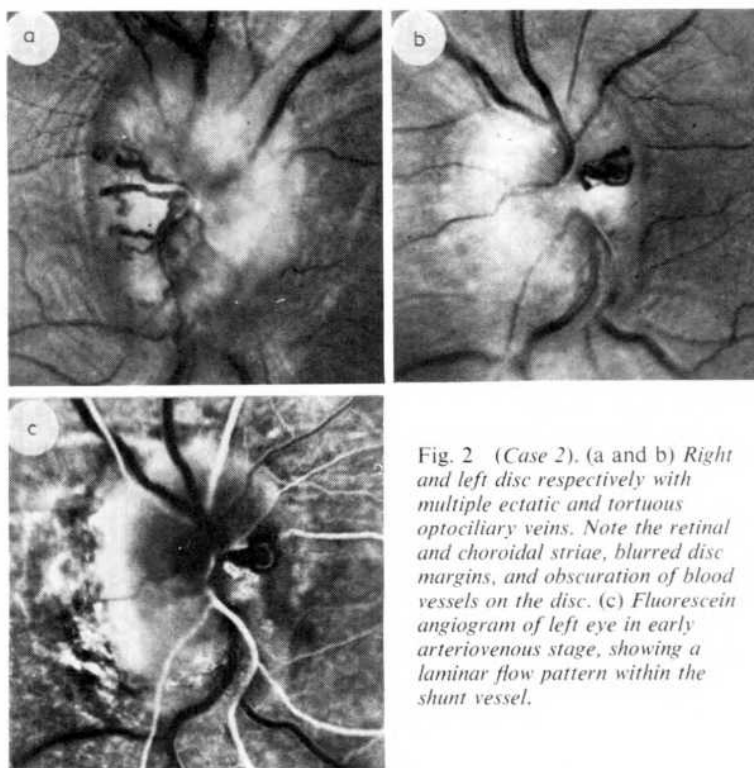


Fig. 2 (Case 2). (a and b) Right and left disc respectively with multiple ectatic and tortuous optociliary veins. Note the retinal and choroidal striae, blurred disc margins, and obscuration of blood vessels on the disc. (c) Fluorescein angiogram of left eye in early arteriovenous stage, showing a laminar flow pattern within the shunt vessel.

compatible with chronic papilloedema. No abnormality was seen after Conray administration. A diagnosis of benign intracranial hypertension was made.

CASE 6

A 25-year-old female was evaluated for headaches of 1 year's duration. One year prior to the onset of headaches she began taking the contraceptive pill. General physical and neurological examinations were normal. Vision was 6/5-2 in each eye, and bilateral, severe papilloedema was present. Cerebrospinal fluid pressure was 400 mm water. Laboratory and radiological studies were all negative. Benign intracranial hypertension was diagnosed and she was treated with steroids. Two and a half years later the left eye had developed a pupillary afferent defect and the vision had declined to 6/12. The left disc showed papilloedema and shunt vessels. The right disc was normal. A lumboperitoneal shunt was inserted.

CASE 7

A 4-year-old boy was seen with bilateral visual deterioration. The boy had Crouzon's disease, and at the age of 2 years had a repair of his cleft palate. On examination he had the characteristic facial

appearances of Crouzon's disease, and in addition there were marked epicanthic folds, the bridge of the nose was underdeveloped, and the orbits were shallow. Vision was hard to assess, but he had vague perception of light on the right and he could see objects and fingers with the left. There was a right relative afferent pupillary defect and ocular movements were full. The right optic disc was grossly pale with multiple shunt optociliary vessels (Fig. 4), and the left disc was slightly pale with several shunt vessels. The child was thought to have raised intracranial pressure with Crouzon's disease.

Discussion

Optociliary shunts may be classified as congenital¹⁹ or acquired. The congenital type shows an anomalous arrangement of the retinal veins, whereas acquired shunts are ectatic and tortuous. Histological studies²⁻⁴ have shown that acquired optociliary shunts connect the retinal venous system to that of the choroid. The laminar flow pattern on fluorescein angiograms conclusively shows that these vessels fill from the retinal venous system. The capillary plexus of the prelaminar region of the disc has its arterial and venous connections largely to

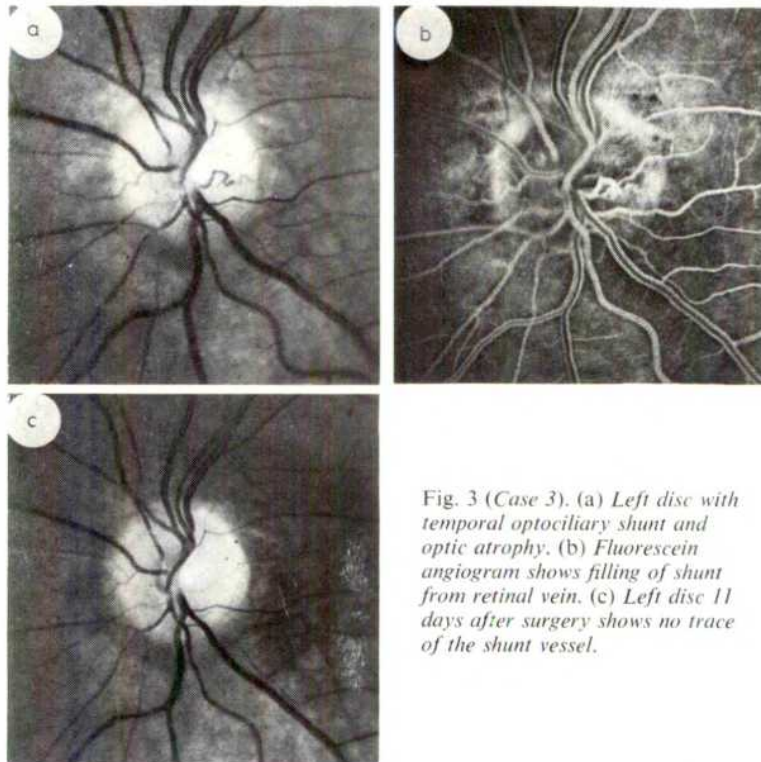


Fig. 3 (Case 3). (a) Left disc with temporal optociliary shunt and optic atrophy. (b) Fluorescein angiogram shows filling of shunt from retinal vein. (c) Left disc 11 days after surgery shows no trace of the shunt vessel.

the adjacent choroid.^{20,21} However, the capillaries of the disc are all interconnected. The central retinal vein communicates with the choroidal circulation in the prelaminar region. Acquired shunts are con-

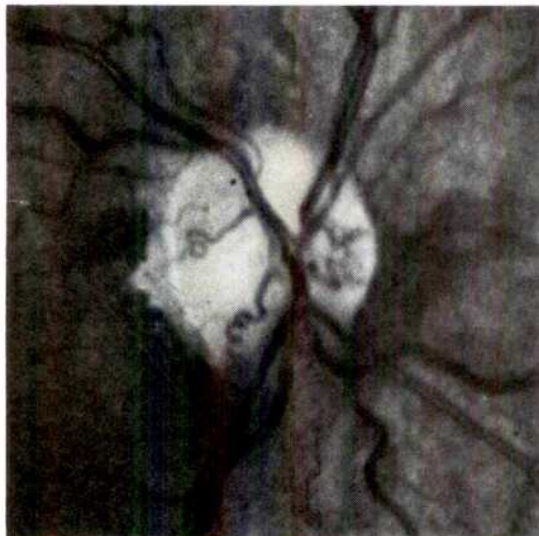


Fig. 4 (Case 7). Right disc with multiple tortuous optociliary shunts and optic atrophy.

ceived as forming through the gradual dilatation and enlargement of anastomotic capillary channels with gradual compression or strangulation of the distal optic nerve sheath and central retinal vein by a tumour or the effects of raised cerebrospinal fluid pressure in papilloedema.

Any optic nerve tumour which is situated sufficiently far forward to obstruct retinal venous drainage directly or through chronic disc oedema would be expected to produce optociliary shunts, given a sufficiently long period of time. It has been shown²⁰ that obstruction of the central retinal vein by itself is insufficient to produce disc oedema. However, the formation of optociliary shunts in papilloedema provides evidence that there is, at least in some cases, an elevation of central retinal venous pressure. It is of interest that in case 3 the shunt vessel disappeared after surgical relief of intracranial pressure, implying its dependence on elevated central retinal venous pressure to remain open.

Each of the patients described above had papilloedema for a prolonged period of time, 2 with intracranial tumours, 4 with benign intracranial hypertension, and 1 with Crouzon's disease. This prolonged oedema may lead to certain changes in the disc tissue, which are referred to as vintage

papilloedema,¹⁷ and eventually the disc may become atrophic. Vintage papilloedema is characterised by shunt vessels and drusen-like bodies at the disc surface or margin which are thought to represent nerve fibre degeneration. Cases 3, 5, and 7 have progressed beyond vintage papilloedema to atrophy with severe visual loss, the shunt vessels remaining as evidence of the preceding prolonged oedema. The triad of tortuous optociliary shunt vessels, prolonged blindness, and a poorly demarcated, atrophic disc may thus arise from papilloedema as well as optic nerve tumour. This triad should not be regarded as specific for optic nerve or sphenoorbital meningioma.¹ These findings were also present in a case of optic nerve arachnoid cyst,⁸ and we have seen optociliary shunts in longstanding cavernous haemangiomas of the orbit and with optic nerve gliomas.

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The Sylvian aqueduct syndrome and neurofibromatosis

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SUMMARY A 23-year-old man initially presented with the Sylvian aqueduct syndrome and subsequently developed cutaneous neurofibromata. The case is reported and the possibility that these represent manifestations of the same genetic abnormality is discussed.

Ophthalmic manifestations of neurofibromatosis are well recognised, and indeed involvement of the eye and its adnexa with neurofibromata has been reported in every structure except the lens and vitreous.¹ However, these are usually seen in the anterior visual system² and reflect the regional hypertrophy of the neural and connective tissue elements that occurs in this condition.³ Abnormalities of the central nervous system are less commonly found in neurofibromatosis, and apart from the well recognised association with optic nerve and chiasmal gliomas⁴ these rarely present to the ophthalmologist. The purpose of this paper is to report a case with the classical neuro-ophthalmic presentation of the Sylvian aqueduct syndrome in which subcutaneous neurofibromata have subsequently developed.

The Sylvian aqueduct syndrome is most commonly due to a pineal tumour, although occasionally encephalitis, vascular occlusion, or a midbrain glioma may produce similar symptoms.⁵ However, the precise diagnosis is usually presumptive, based on the presence of associated clinical signs and a successful trial of radiotherapy, since surgical exploration is still hazardous in this area. In the case under review the original presentation was thought typical of a pineal tumour. However, the subsequent development of characteristic cutaneous stigmata suggests that the initial midbrain syndrome was an unusual manifestation of neurofibromatosis. So far as we are aware this association has not previously been reported.

Case report

A 23-year-old man was admitted to hospital in May 1969 with symptoms of raised intracranial pressure and diplopia. He had first presented to an optician

9 months earlier complaining of difficulty with his distance vision. He was prescribed a small myopic correction for distance vision in both eyes, with initial improvement. However, 2 months before admission he began to have difficulty with near vision and to notice vertical diplopia. Both these symptoms persisted, and in addition he developed severe headaches and vomiting, which precipitated his admission.

On examination he was found to have a correctable vision of 6/5, N5 in each eye. There was a dissociated deficit of upgaze with relative loss of saccadic movement but preservation of smooth pursuit movement. Attempts at rapid upward saccades evoked convergence retraction nystagmus. A skew deviation was present, with left hypotropia. The pupillary responses showed light near dissociation. There was bilateral chronic papilloedema. A clinical diagnosis of the Sylvian aqueduct syndrome was made.

Investigation by pneumoencephalography revealed symmetrical hydrocephalus (Fig. 1) with obstruction of the Sylvian aqueduct (Fig. 2). A Torkildsen shunt was performed and the midbrain region treated with 5000 rads in divided doses. His symptoms of raised intracranial pressure were rapidly relieved, but the oculomotor and pupillary disturbance have persisted.

He had no further problems until 1976, when he presented to the Skin Department with small painless lumps on his abdomen; these had appeared over the previous year. A biopsy of one of them showed the typical features of neurofibromata (Fig. 3). Since then these lesions have remained unchanged.

Discussion

The Sylvian aqueduct syndrome is a classical constellation of neuro-ophthalmological signs which

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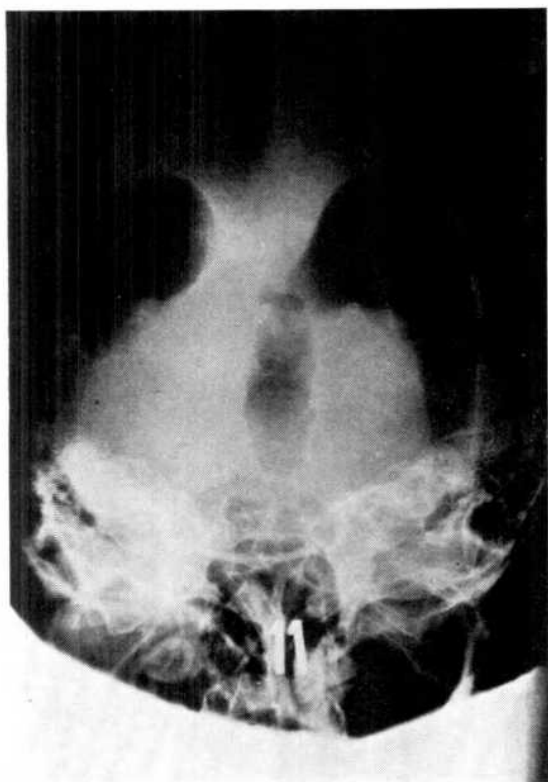


Fig. 1 Air ventriculogram. Towne's projection. There is marked hydrocephalus, with considerable enlargement of the third ventricle.

were initially described by Parinaud and attributed to compression of the pretectal region. The initial presentation of this patient with acquired myopia is unusual but well recorded.⁶ The commonest cause of the syndrome is a pineal tumour, of which the majority are atypical teratomas.⁷ However, in a recent series of neurosurgical explorations 25% of tumours in this region were found to be nonpineal in origin.⁸ In this patient the development of cutaneous neurofibromata 8 years after the original midbrain syndrome suggests that the 2 lesions are related and the underlying pathology the same.

Abnormalities of the central nervous system are well recognised in neurofibromatosis. The incidence in published series ranges from 3%⁹ to 19%.¹⁰ A wide range of abnormalities have been reported, from neoplastic gliomata to glial heterotopias and other dysplastic malformations. The most frequently found glioma is the optic nerve and chiasmal astrocytoma of childhood,⁴ but similar gliomata occur in the intracranial cavity, either as single¹¹ or as multiple lesions^{12,13} and occasionally as diffusely infiltrative tumours.¹⁴ Meningiomas are also associated, and they may be multiple.¹⁵ Non-neoplastic malformations of the central nervous system are also regularly found in neurofibromatosis and have recently been extensively reviewed.¹⁶ These central forms of neurofibromatosis are often found in the absence of extensive peripheral disease. Indeed, to some extent the peripheral and central manifestations of neurofibromatosis are mutually exclusive.¹⁷ In a recent review of 10 cases of neurofibromatosis

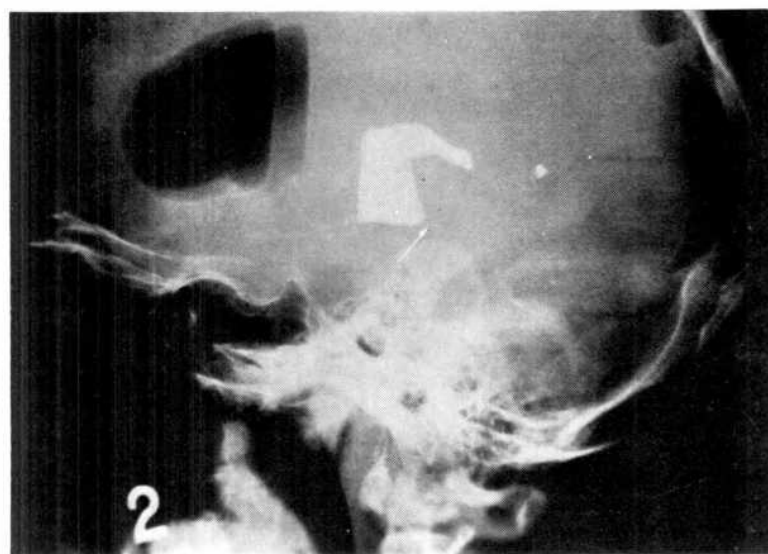
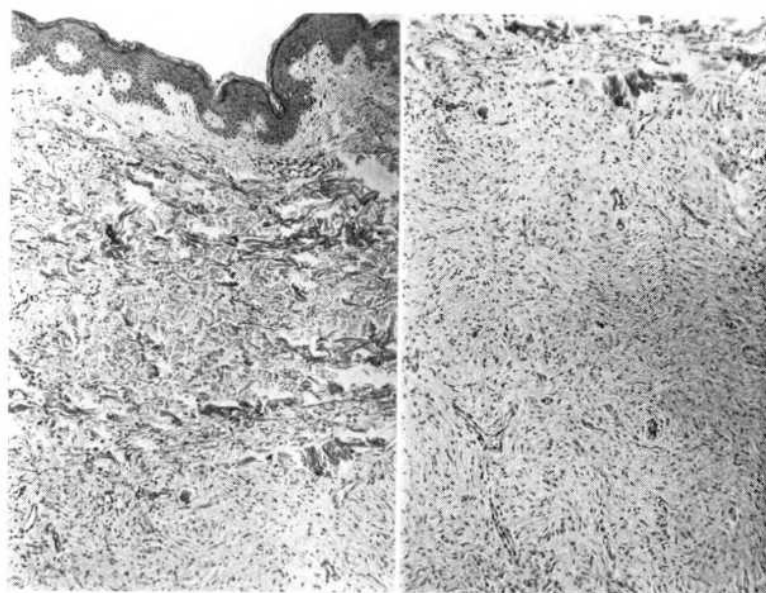


Fig. 2 Lateral projection, 'brow up' position. Iophendylate (Myodil) has now been injected. It outlines the posterior end of the third ventricle and the dilated upper portion of the Sylvian aqueduct, but does not pass beyond this (arrow). The suprapineal recess is prominent, but there is no evidence of an extrinsic mass lesion. The appearances are those of occlusion of the aqueduct.

Fig. 3 A composite photomicrograph showing an extensive neurofibroma in the deeper levels of the reticular dermis. ($\times 75$.)



with tumours of the central nervous system 4 showed no cutaneous disease, while the remaining 6 had only limited skin pigmentation and a few subcutaneous nodules.¹⁸ The paucity of cutaneous stigmata in the case under review is therefore entirely compatible with an underlying diagnosis of neurofibromatosis.

However, despite the extensively described involvement of the central nervous system in neurofibromatosis we have been unable to find a previous example presenting with the neuro-ophthalmic signs of the Sylvian aqueduct syndrome. The only clinically similar case in the literature presented the pathology of Sylvian aqueduct stenosis in an 11-year-old girl with cutaneous pigmentation, a convergent squint, poorly reacting pupils, and bilateral sixth nerve weakness. Clinical photographs in this report appear to show a skew deviation, but no further neuro-ophthalmological information is available. The obstructed aqueduct was found to have polypoid ependymal granulations beneath the posterior colliculus.¹⁹ One other case report has documented isolated stenosis of the Sylvian aqueduct in neurofibromatosis but without the characteristic eye movement disorder of the Sylvian aqueduct syndrome.²⁰

Without a definite biopsy the exact relationship between the midbrain pathology and peripheral neurofibromata in this case must remain conjectural. However, it seems likely that they are manifestations of the same genetic abnormality. It has recently been suggested that all the protean manifestations of von Recklinghausen's disease may result from primary dysontogenesis of primitive

neural ectoderm and neural crest derivatives.³ By proliferation, differentiation, and migration cells of the neural crest form a major component of the adult nervous system. The sensory and autonomic ganglia, leptomeninges, Schwann cells, and some supportive connective tissue elements are all derived from this embryonic tissue. In addition some glial and neurilemmal cells of the central nervous system may arise from the neural crest or may originate as a distinct cell population in the neural folds.²¹ Dysplastic or frankly neoplastic change in this second group of cells is thought to be responsible for the lesions seen in central forms of neurofibromatosis. In the case under review the absence of progression suggests that dysplasia of these central glial or neurilemmal cells is the most likely cause of the midbrain syndrome, and furthermore, that a common origin in neural ectoderm forms the link between these 2 apparently unrelated clinical symptoms.

I am grateful to Professor John Marshall for permission to publish details of this case and to Mr M. D. Sanders for helpful criticism in the preparation of the text. Dr Ivan Moseley kindly provided the radiographic reports, and the Department of Dermatology, St Thomas's Hospital, provided histopathology of the skin biopsy. My thanks are also due to Miss Denise Bryant for secretarial assistance.

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Comparative sensitivity of fluorescent antibody staining of conjunctival scrapings and irradiated McCoy cell culture for the diagnosis of hyperendemic trachoma

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SUMMARY The sensitivity of an indirect fluorescent antibody (FA) staining technique for detecting chlamydial inclusions in scrapings from the whole conjunctiva (upper tarsus, upper fornix, and lower lid) was compared with the sensitivity of culture in irradiated McCoy cells for the diagnosis of hyperendemic trachoma. In a group of 211 patients with various grades of active trachoma from the Bandar Abbas area of Southern Iran 42 patients were positive for chlamydiae by either method. There was little difference between the rates of positivity of FA staining of the scrapings from the whole conjunctiva (28 positives) and culture in irradiated McCoy cells (32 positives). In the patients included in this study chlamydial inclusions were detected in 15 eyes by examination of FA stained scrapings taken from the upper tarsal conjunctiva, whereas inclusions were detected in 40 eyes by the additional examination of scrapings taken from the upper fornix and lower lid ($P < 0.001$). The examination of FA stained scrapings taken from the whole conjunctiva and spread as a single but larger smear may provide a satisfactory alternative to cell culture methods for the diagnosis of trachoma, particularly for field studies when cell culture facilities are not available.

Laboratory tests which provide support for field studies of hyperendemic trachoma include the direct demonstration of chlamydial inclusions in conjunctival scrapings and cultural tests. The fluorescent antibody (FA) staining technique is more sensitive than the traditional method of Giemsa staining for the detection of chlamydial inclusions in conjunctival scrapings.¹⁻⁴ Culture in irradiated McCoy cells is more sensitive than the direct demonstration of chlamydial inclusions in Giemsa stained smears for the diagnosis of hyperendemic trachoma as well as paratrachoma of sexually transmitted origin.¹

The aims of the present study were to investigate the prevalence of chlamydial inclusions detected by FA staining in scrapings from the different areas of the conjunctiva and to compare the sensitivity of FA staining of scrapings from the upper tarsus as well as the whole conjunctiva with that of irra-

diated McCoy cell culture for the detection of *Chlamydia trachomatis* in cases of hyperendemic trachoma.

Materials and methods

SELECTION OF PATIENTS

Patients with different grades of active trachomatous inflammatory changes in their eyes⁵ were selected from 2 villages in the Bandar Abbas area of Southern Iran. These patients were part of a study on the natural history and transmission of hyperendemic trachoma in their villages.

COLLECTION OF SPECIMENS

Conjunctival swabbings were collected from the whole conjunctiva (i.e., the upper tarsus, upper fornix, and lower lid) of each eye as described by Darougar *et al.*⁶ Right and left paired specimens were pooled in a plastic capsule containing 2SP transport medium⁷ with additional 3% fetal bovine serum. All conjunctival swabbings were stored

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immediately in a portable liquid nitrogen refrigerator at -180°C for transport to the Virus Laboratory, London, where they were subsequently stored in a refrigerator at -70°C until inoculated into cell cultures.

After swabbing, conjunctival scrapings were collected separately from the upper tarsus, upper fornix, and lower lid of each eye with sterile aluminium scrapers.⁶ The material collected from each area was spread thinly and evenly within 6 mm diameter areas scratched on clean glass microscope slides. Scrapings were air dried and fixed in methyl alcohol for 5 minutes at room temperature. Transport to London (4 or 5 days) was at ambient temperature, after which slides were stored at -20°C until stained.

CELL CULTURE

The simplified technique of culture in irradiated McCoy cells as described by Darougar *et al.*⁸ was used. Monolayers were fixed after 60–72 hours incubation, stained with Giemsa, and examined by dark-field illumination.

FLUORESCENT ANTIBODY STAINING

The conjunctival scrapings were stained by the indirect method of FA staining.⁹ The antiserum used, a hyperimmune rabbit serum against an LGV strain (LGV/2/USA/Cal-434/Bu), was produced at the Institute of Ophthalmology by multiple intravenous injections of agent over several months. The stained preparations were examined with a Zeiss standard fluorescence microscope fitted with an HBO 200 mercury vapour lamp and dark-field condenser. Exciter filter BG12 and barrier filters 50 and 44 were used. Bright green, sharply circumscribed inclusions within the cytoplasm of epithelial cells were identified as chlamydial inclusions. The total number of inclusions detected in each smear was recorded.

McNemar's test and paired sample *t* test were used for comparison of the results.

Results

Of a total of 211 patients included in this study 42 patients (20%) were positive by either FA or cell culture (Table 1). Of these 42 positive patients 28 (67%) were positive by FA staining of scrapings from the whole conjunctiva, 12 (29%) were positive by the examination of scrapings from the upper tarsus alone (the traditional method), and 32 (76%) were positive by the irradiated McCoy cell culture method. The examination of FA stained scrapings from the upper tarsus alone was significantly less sensitive than cell culture ($P < 0.001$), but the

Table 1 *Comparative sensitivity of FA staining of scrapings from the whole conjunctiva and culture in irradiated McCoy cells in 42 patients positive for chlamydiae by either method*

	Number of patients
Positive by cell culture	32 (76%)
Positive by FA	28 (67%)
Positive by FA and culture	18 (43%)
FA positive, culture negative	10* (24%)
FA negative, culture positive	14 (33%)

*The number of inclusions detected was fewer than 6 in 9 patients, whereas in the other patients it was 39.

Table 2 *Comparison of scrapings from different areas of the conjunctiva for the detection of chlamydial inclusions in 40 positive eyes*

Source	Number of positive scrapings	Total number of inclusions
Upper tarsus (UT)	15 (38%)	60
Upper fornix (UF)	24 (60%)	81
Lower lid (LL)	28 (70%)	96
Whole eye* (UT + UF + LL)	40 (100%)	237

*The figures for the whole eye were obtained by combining the results for each individual area.

difference between the sensitivities of cell culture and FA staining of scrapings from the whole conjunctiva was not statistically significant ($P > 0.5$).

In 28 patients who were positive by FA staining chlamydial inclusions were detected in conjunctival scrapings from 40 eyes. The number of positive smears from different areas of the conjunctiva and the numbers of inclusions detected in these 40 eyes are shown in Table 2. The lower lid showed the highest rate of 70% positivity (28 out of 40) with an average number of 2.4 inclusions per smear, whereas the upper tarsus was positive in only 38% (15 out of 40) with an average number of 1.5 inclusions. The difference between the rates of positivity of the upper tarsus and the lower lid is statistically significant ($P < 0.01$). The number of inclusions seen in scrapings taken from the different areas of the conjunctiva were not significantly different from one another ($P > 0.1$). In the case of only one eye was the scraping from the upper tarsus positive, while those from the upper fornix and the lower lid were negative. The examination of scrapings from the 3 different areas of the conjunctiva was significantly more sensitive than the examination of scrapings from any one area alone ($P < 0.001$). However, the addition of the results obtained from

the upper tarsus scrapings did not significantly increase the sensitivity obtained by the examination of only the upper fornix and lower lid scrapings ($P > 0.05$).

Discussion

There was little difference between the sensitivities of cell culture and FA staining of scrapings from the whole conjunctiva for the diagnosis of trachoma. In this study the conjunctivae were swabbed for culture before scraping, which may have reduced the rate of detection of inclusions in the scrapings, especially where few inclusions were present. However, studies in London have shown that the order in which conjunctival scrapings and swabbings are collected has little effect on the rate of positivity of either type of specimen.¹⁰

For FA staining the World Health Organisation¹¹ recommends fixation in acetone, transport on wet ice, and storage at -20°C . In this investigation scrapings were fixed in methyl alcohol and transported to London at ambient temperature, a method which is not considered optimum for subsequent FA staining. It is therefore possible that some inclusions present in the scrapings were not detected.

The World Health Organisation¹¹ recommends that conjunctival scrapings are taken from only the upper tarsus. The results of this study indicate that scrapings from this area are the least sensitive for the detection of inclusions. Scrapings from the upper fornix and the lower lid were almost twice as sensitive as scrapings from the upper tarsus for the diagnosis of trachoma. However, for maximum sensitivity, scrapings should be taken from all areas of the conjunctiva. In this study only 1 eye had inclusions in the upper tarsus alone, and it may therefore be possible to exclude the upper tarsus scrapings without significantly reducing the sensitivity of the test.

The time required for the examination of a single FA stained scraping is approximately the same as for the examination of a McCoy cell monolayer. The examination of scrapings from different areas of the conjunctiva is therefore more time-consuming than the cell culture method. However, if material taken from different areas were spread on a single but larger smear, there should be little difference between the times taken for the 2 methods. The time needed to prepare the specimens for examination is similar for either method, but conjunctival scrapings can be stained by the FA technique immediately and results can be obtained within 2 to 3 hours of fixation.

While cell culture is the method of choice for the diagnosis of chlamydial infections, an established

laboratory with experienced technicians and adequate facilities for the transport of specimens while frozen is required for this method. However, FA staining of scrapings from the whole conjunctiva offers a satisfactory alternative for which the main requirements are antisera and a fluorescence microscope, and may therefore be better suited for studies in the field where facilities for cultural tests are not generally available. The use of both FA and cell culture procedures is to be recommended if maximum sensitivity is required.

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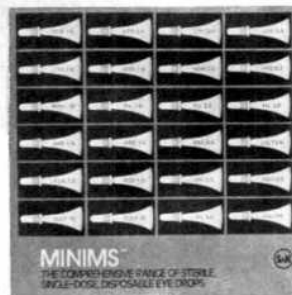
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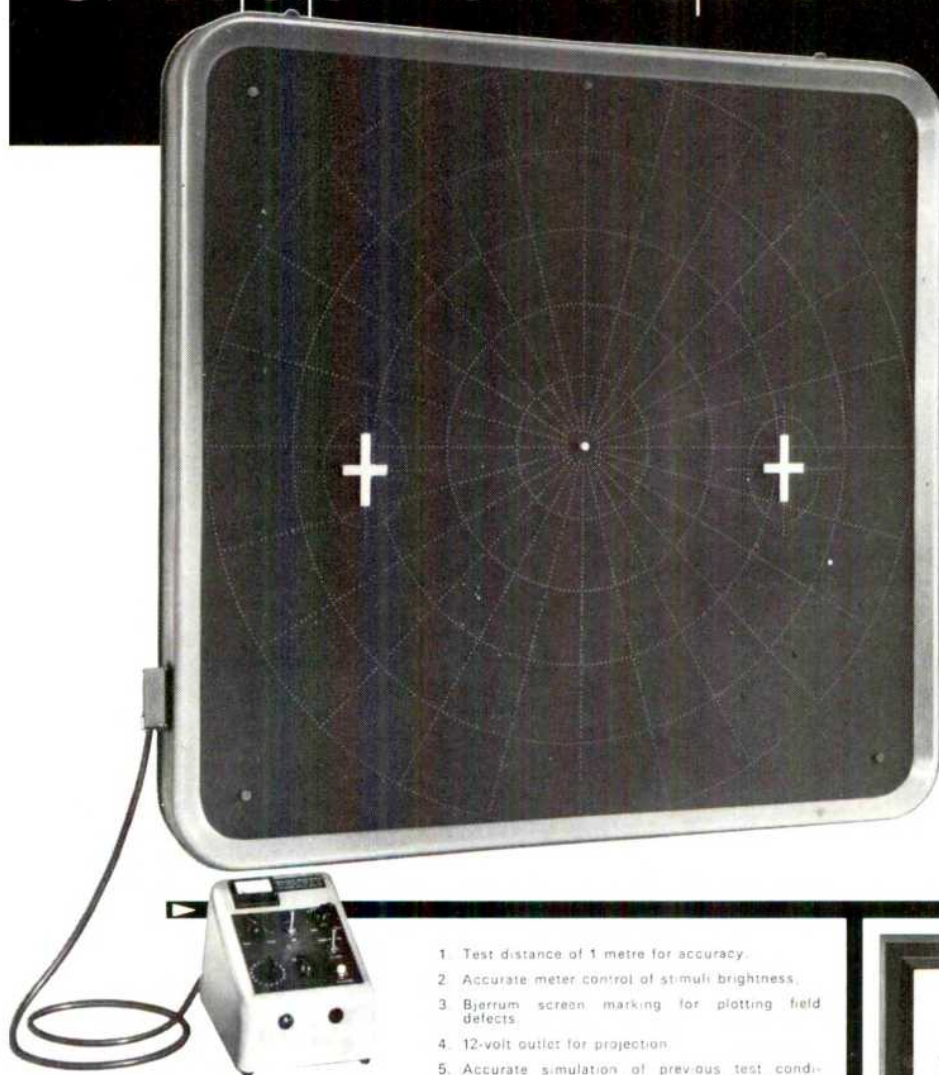
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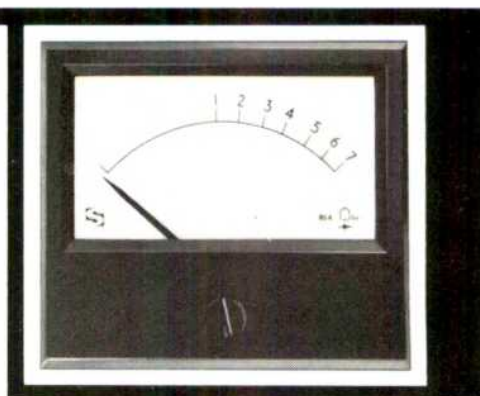
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Guinea-pig inclusion conjunctivitis as a model for the study of trachoma: clinical, microbiological, serological, and cytological studies of primary infection

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SUMMARY The course of primary ocular infection with guinea-pig inclusion conjunctivitis agent was followed in 2 groups of animals. One group of fully grown animals was repeatedly scraped; the other of small animals was used on 1 occasion only and scraped after clinical examination. The intensity of conjunctival inflammation was measured, conjunctival scrapings were taken, and the numbers of polymorphonuclear cells, mononuclear cells, and epithelial cells containing chlamydial inclusions were counted, and the level of antibodies in serum was measured. It was found that inflammation of the conjunctiva lasted for about 30 to 40 days, and the clinical features (oedema, hyperaemia, papillary reaction) were very similar in the 2 groups. Inclusions and polymorphonuclear cells were found for up to 21 days, and mononuclear cells were found on days 7 to 25. Serum antibodies were first detected on day 10 and reached a peak on day 21. The intensity of inflammation was significantly higher on day 2 in the animals which had been scraped. After this the severity of the inflammation and the course of disease were similar in the 2 groups.

Guinea-pig inclusion conjunctivitis (GPIC) is a naturally occurring disease of guinea-pigs, caused by a member of the species *Chlamydia psittaci*.^{1,2} Kazdan *et al.*³ described the clinical features of naturally occurring and experimentally induced disease. Treharne⁴ measured the number of inclusions and inflammatory cells in conjunctival scrapings taken at various stages of the disease and the levels of antichlamydial antibodies in sera.

In this study we have looked at the clinical aspects of primary ocular infection, quantified the intensity of inflammation, and attempted to correlate this with the microbiological, cytological, and serological findings.

Materials and methods

ANIMALS

Female albino guinea-pigs of the Dunkin-Hartley strain were used. Those in the first experiment were fully grown animals weighing 600 to 700 g,

those in the second experiment weighed 220 to 250 g at the start of the experiment.

ORGANISMS AND INFECTION

GPIC agent, strain A10, grown in the yolk sacs of embryonated hens' eggs, was used. Animals were infected by putting 1 drop of inoculum (containing 10⁶ EID₅₀) on to the conjunctiva.

CLINICAL ASSESSMENT OF ACTIVE INFLAMMATION

Animals were examined with a Zeiss Surgery Microscope II (Carl Zeiss, Jena). The upper and lower lids, bulbar conjunctiva, limbus, cornea, and palpebral conjunctivae were examined, and intensity of inflammatory changes was scored as mild (1), moderate (2), and severe (3). The maximum possible score per eye was 69 as shown in Table 1.

CONJUNCTIVAL SCRAPINGS

The left eye was anaesthetised with 1 drop of Novesine solution (0.4% benoxinate hydrochloride and 0.01% chlorhexidine acetate). The eye was

Table 1 *Maximum scores of signs observed in guinea-pig inclusion conjunctivitis*

		Maximum score
Discharge		3
Lacrimation		3
Lid	Erythema (upper)	3
	" (lower)	3
	Swelling (upper)	3
	" (lower)	3
Bulbar conjunctiva	Hyperaemia	3
	Chemosis	3
Limbus	Oedema	3
	Follicles	3
Cornea	Diffuse superficial keratitis	3
Palpebral conjunctiva	Hyperaemia (upper)	3
	" (lower)	3
	Oedema (upper)	3
	" (lower)	3
	Papillae (upper)	3
	" (lower)	3
	Follicles (size $\times$ area) (upper)	9
	" " " (lower)	9
Maximum total score		69

blotted dry with a clean tissue and the upper and lower tarsal areas were scraped with an aluminium scraper. Scrapings were spread on slides, air dried, methanol fixed, and stained with Giemsa stain. Conjunctival scrapings were examined microscopically, at a magnification of $\times 400$, and the numbers of conjunctival epithelial cells, inclusion-bearing epithelial cells, polymorphonuclear cells, and mononuclear cells (lymphocytes, lymphoblasts, plasma cells, monocytes, and macrophages) in at least 5 nonadjacent microscope fields were counted. The results were expressed as the percentage of epithelial cells containing inclusions, and the number of mononuclear cells or polymorphonuclear cells per 100 epithelial cells.⁴

SERUM ANTIBODIES AGAINST GPIC AGENT

Blood was collected by cardiac puncture and allowed to clot. The serum was separated by centrifugation and stored at -20°C . Total antichlamydial antibodies were measured by an indirect micro-immunofluorescence test¹ using antigen plaques of egg-grown GPIC agent and uninfected yolk-sac material as a control. Fluorescein isothiocyanate-labelled rabbit anti-guinea-pig whole globulin (GIBCO: Bio-Cult Ltd.) was used as a conjugate, with rhodamine-labelled bovine serum albumin (DIFCO) as a counterstain. The first dilution of serum was 1/8, and only bright apple-green fluorescing particles were read as positive.

EXPERIMENTAL DESIGN

The first experiment was carried out on 5 fully grown animals, infected in the left eye, which was examined, photographed, and scraped immediately before infection and at intervals after infection. The second experiment was carried out on 40 young guinea-pigs. Fresh groups of 4 animals were taken immediately before infection and at various intervals after infection, eyes were examined, photographed, and scraped, and blood collected by cardiac puncture for serological testing.

STATISTICS

Student's *t* test, modified for comparison of small samples, was used.⁵

Results

INCUBATION PERIOD

In both experiments the incubation period was less than 2 days.

DURATION AND SEVERITY

The duration of conjunctival inflammation was 21 to 40 days with a mean duration of 30 days. In the first experiment there was a large increase in the intensity of inflammation on day 2. This gradually decreased until day 7, increased for a further week, and then declined (Fig. 1a). In the second experiment the intensity of inflammation observed on day 2 was significantly lower than in the first experiment ($P < 0.001$). The responses seen from day 4 onward were very similar to those seen in the first group (Fig. 1a).

SIGNS

A mild to moderate lacrimation and discharge were present throughout the infection in both groups of animals. Erythema and swelling of the lids was observed on day 2 in all 5 animals in the first experiment and persisted in some animals until day 21. In the second experiment these signs were not as common or as severe.

In the bulbar conjunctiva moderate to severe oedema was present from day 2 to day 21 in both groups of animals, and mild oedema was still present on day 35 in the second group (Fig. 2a). In the first experiment moderate hyperaemia was observed from day 2 to day 10, and very mild hyperaemia was still present on day 25. In the second experiment no hyperaemia was seen until day 4, and mild hyperaemia persisted until day 35 (Fig. 2b).

In the palpebral conjunctivae the severity of hyperaemia, diffuse infiltration, and papillary hypertrophy was the same in upper and lower lids. The

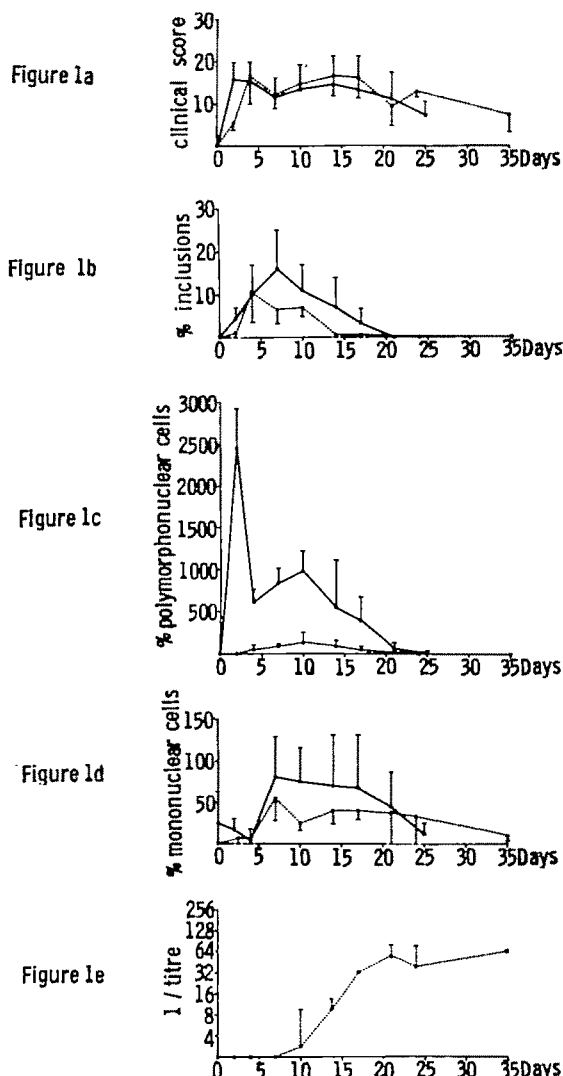


Fig. 1 The course of infection in 2 groups of animals (mean + standard deviation). Solid line = animals repeatedly scraped; dashed line = animals infected without scraping and used on 1 occasion only.

pattern of response was very similar in the 2 experiments. Moderate hyperaemia, diffuse infiltration, and papillary hypertrophy were first seen on day 2, were most severe from day 7 to day 17, and then declined (Figs. 2c, 2d, 2e). No follicles or conjunctival scars were found.

Corneal vessels, which are normally present,* became congested during the acute phase of the infection, but no pannus (neovascularisation and cellular infiltration of the cornea) was observed. A mild, diffuse epithelial and subepithelial keratitis

of the upper half of the cornea occurred sporadically.

CHLAMYDIAL INCLUSIONS

No inclusions were found in scrapings taken before infection. In the first experiment, in which animals were scraped immediately before infection, the percentages of epithelial cells containing inclusions increased on days 2 and 4, reaching a peak on day 7 (mean 16%). The percentage then declined steadily, and no inclusions were seen on day 21 (Fig. 1b). In the second experiment, in which animals were not scraped before infection, the percentage of inclusions seen on day 2 was significantly lower than in the first experiment ($0.01 > P > 0.002$). The highest level (mean 10.5%) was seen on day 4, and there was a decrease on day 7, when the percentage of inclusions was again significantly lower than in the first experiment ($0.02 > P > 0.01$). There was a

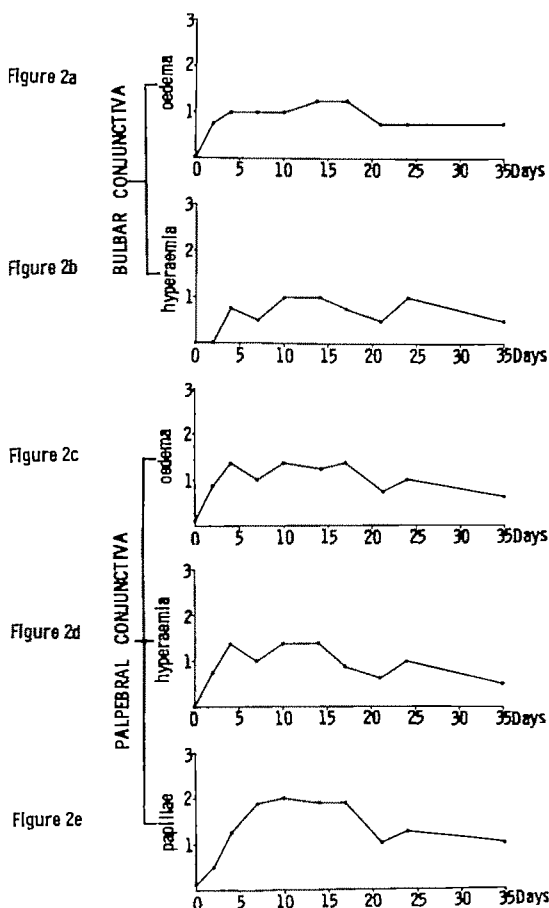


Fig. 2 Intensity and duration of signs in unscraped animals.

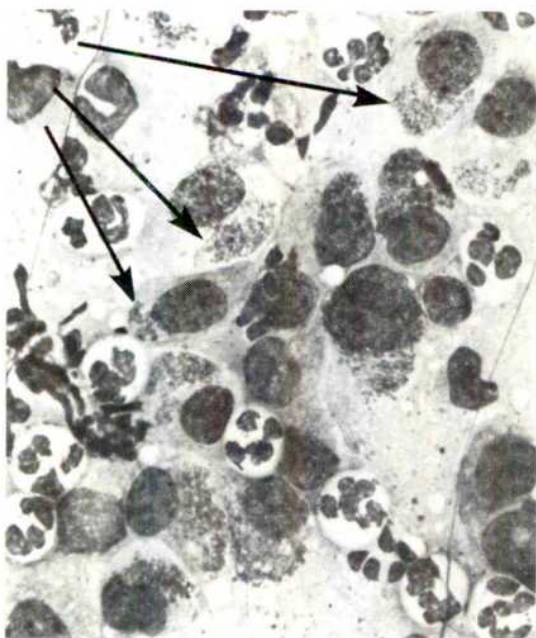


Fig. 3 Scraping taken 4 days after infection showing several inclusions in adjacent conjunctival epithelial cells (arrowed), many polymorphonuclear cells, and a few lymphocytes ($\times 670$).

further decrease between days 10 and 14, and no inclusions were seen after day 17 (Fig. 1b).

At the peak of infection, when a large number of cells were infected, inclusions were found in groups of adjacent epithelial cells (Fig. 3).

POLYMPHONUCLEAR CELLS

Polymorphonuclear cells were rarely seen in scrapings from normal eyes. Those seen during infection consisted almost entirely of neutrophilic cells; eosinophils and basophils were very rarely seen. In the first experiment there was a massive increase in the level of polymorphonuclear cells following inoculation, with a mean peak value of 2450% on day 2, followed by a large reduction on day 4 (Fig. 1c). There was a second peak on day 10 (mean level 980%), after which the number of cells steadily declined, returning to normal levels by day 25. In the second experiment there was a much smaller increase in neutrophils, with a mean peak level of 130% on day 10, followed by a gradual decrease, returning to normal levels on day 21 (Fig. 1c).

MONONUCLEAR CELLS

A few mononuclear cells were seen before infection in the animals used in the first experiment. In both experiments the number of mononuclear cells

increased significantly between days 4 and 7 ($0.02 > P > 0.01$), to reach mean peak levels of 80% and 55% respectively (Fig. 1d). Lymphocytes predominated, though some lymphoblasts, plasma cells, macrophages, and monocytes were also seen. In the first experiment the number of cells remained high (45% to 75%) until day 21, and returned to preinfection levels by day 25. In the second experiment relatively high numbers were seen on days 10 to 24 (25% to 40%); at day 35 the mean level was 10%.

SERUM ANTIBODIES

Total serum antibodies against GPIC agent were measured in the animals used in the second experiment. No antibodies were present on day 0, and none were detected until day 10, when 2 out of 4 animals were positive at the first dilution (1/8). On day 14 all 4 sera contained antibodies, and there were further increases on day 17 and 21. On day 35 all 4 animals had levels of 1 in 64 (Fig. 1e).

Discussion

There are 2 features of the normal guinea-pig eye which have led to some confusion when clinical signs in guinea-pig eyes have been compared with signs in man. Firstly, the normal guinea-pig eye has superficial corneal vessels which extend from the limbus toward the centre of the cornea; these can be seen with the aid of an operating microscope or slit-lamp. When the eye is infected, these vessels dilate and are more easily seen, but should not be mistaken for pannus. Secondly, there are masses of lymphoid tissue in the upper and lower palpebral conjunctivae of the normal guinea-pig, which are also found in the fetal guinea-pig,⁶ and they should not therefore be mistaken for the follicles which develop on the conjunctivae in trachoma. In the experiments described here we observed what appeared to be follicles, which on histological examination proved to be the normal folds of the conjunctiva, swollen during infection (unpublished results).

The clinical signs and the course of the disease were very similar in the 2 groups of animals. It is evident that changes in the intensity of inflammation were not directly related to changes in the numbers of inclusions, polymorphonuclear cells, or mononuclear cells alone. Different patterns of cellular reaction were seen at different stages of the disease. The percentage of epithelial cells containing inclusions reached a peak early in the disease (days 4 to 7) and then decreased; none were seen after about day 20. Increased levels of polymorphonuclear cells were found only when inclusions were also present.

The mononuclear cells had a different pattern of behaviour from polymorphonuclear cells and inclusions; few were seen until day 7, when a sharp increase occurred. High levels were maintained until about day 20. It is interesting to note that after the increase in mononuclear cells on day 7 the percentage of epithelial cells containing inclusions decreased, and the high level of mononuclear cells was maintained until no more inclusions were found. Antichlamydial antibodies were not consistently found until day 14, when the number of inclusions had already decreased. These results are similar to those of Treharne,⁴ who found the highest percentage of epithelial cells containing inclusions on days 4 to 8, whereas antibody titres of 1/8 or more were not found in all animals until day 15.

The role of trauma on primary ocular infection was examined by comparing the 2 experiments, one using animals which were scraped repeatedly, the other using animals which were not scraped. The levels of inflammation were very similar in the 2 groups of animals except on day 2, when the levels of inflammation, polymorphonuclear cells, and inclusion-containing epithelial cells were significantly higher in the scraped group. Although the levels of inflammation after day 2 were very similar in the 2 groups, the level of inclusions was generally higher in the scraped group of animals, and this was associated with higher levels of inflammatory cells, particularly polymorphonuclear cells. We therefore conclude that the major effect of scraping is on the very early stages of infection. When adult human volunteers were inoculated with strains of

C. trachomatis isolated from 2 babies with ophthalmia neonatorum, Jawetz *et al.*⁷ found that scraping had no effect on the susceptibility of the conjunctiva to infection or the course of the disease.

In the following paper⁸ we describe the effects of reinfection with GPIC agent, which produces chronic disease and lesions similar to those of trachoma.

We thank Professors Barrie Jones and John Turk for helpful discussions, and the Medical Research Council and an anonymous donor for financial support.

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Development of chronic conjunctivitis with scarring and pannus, resembling trachoma, in guinea-pigs

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SUMMARY Guinea-pigs were repeatedly infected with guinea-pig inclusion conjunctivitis agent. Reinfection caused severe conjunctival inflammation, and repeated reinfection led to chronic inflammation lasting for many months. This was followed by the development of pannus, follicles on the palpebral conjunctivae, scarring of the lower palpebral conjunctiva, and deformities of the lower lid. Reinfection was accompanied by small numbers of inclusion-bearing cells, small numbers of polymorphonuclear cells, and high numbers of mononuclear cells. There was no increase in the level of serum antibodies. The chronic conjunctivitis was associated with high numbers of mononuclear cells and no inclusions or polymorphonuclear cells. The response to reinfection appears to be a delayed-type hypersensitivity reaction, and we suggest that the chronic inflammation, pannus, scarring, and lid deformities associated with hyperendemic trachoma may be due to repeated reinfection combined with delayed-type hypersensitivity.

Primary ocular infection with guinea-pig inclusion conjunctivitis (GPIC) agent produces acute conjunctivitis, with no pannus or scarring, which resolves spontaneously in 30 to 40 days.^{1–3} It has not therefore been considered a good model for trachoma.

In this study we have looked at the ocular responses of guinea-pigs to reinfection with GPIC agent, and compared them with the responses to primary infection. We have found that repeated reinfection produces chronic conjunctivitis with scarring and pannus, similar to trachoma.

Materials and methods

Animals, organisms, methods for clinical assessment, conjunctival scrapings and serology are described in the previous paper.³

EXPERIMENTAL DESIGN

Animals were infected and reinfected in the left eye, with 1 drop of inoculum (containing 10^6 EID₅₀ of GPIC agent strain A10) as described in the previous paper.³

The first experiment was carried out on 5 fully-grown animals, which were examined, photographed

and scraped immediately before infection and at intervals after infection and reinfection. These animals were infected 7 times.

The second experiment was carried out on 128 young guinea-pigs. Fresh groups of 4 animals were taken immediately before infection and at various intervals after infection and reinfection; eyes were examined, photographed and scraped, and blood collected for serology. These animals were infected 5 times.

Results

DURATION AND SEVERITY OF DISEASE

In the first experiment the duration of conjunctival inflammation increased in successive infections (Fig. 1*d*). After the seventh infection inflammation persisted for over a year.

In the second experiment (Fig. 2*e*) infections were carried out at 35- and 28-day intervals, when inflammation from previous infections was still present.

In both experiments the severity of inflammation was generally greater during reinfection (Figs. 1*d*, 2*e*). In the early reinfections there was acute, severe inflammation lasting for 4 to 7 days (Fig. 5), followed by a mild to moderate inflammation, lasting several weeks or months. In later infections the

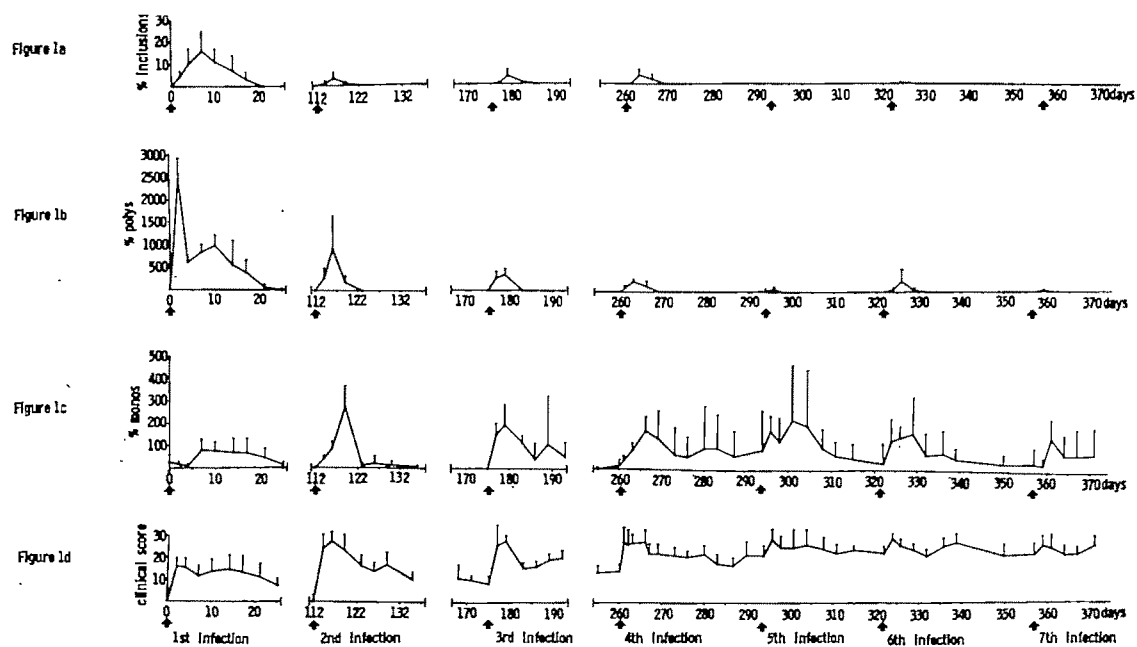


Fig. 1 The responses of 5 animals to 7 successive GPIC agent infections (mean + standard deviation). Arrows indicate inoculations.

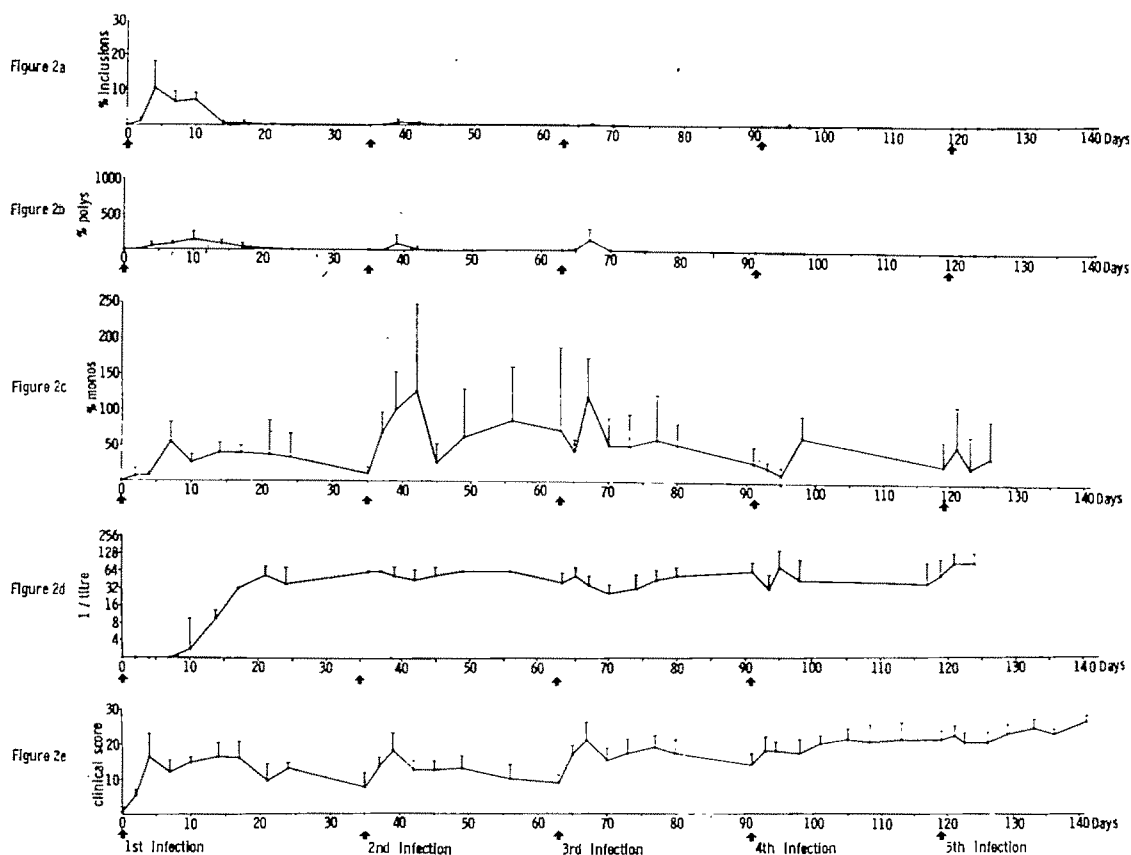


Fig. 2 The responses of groups of 4 animals, which had not previously been scraped, to 5 successive GPIC agent infections (mean + standard deviation). Arrows indicate inoculations.

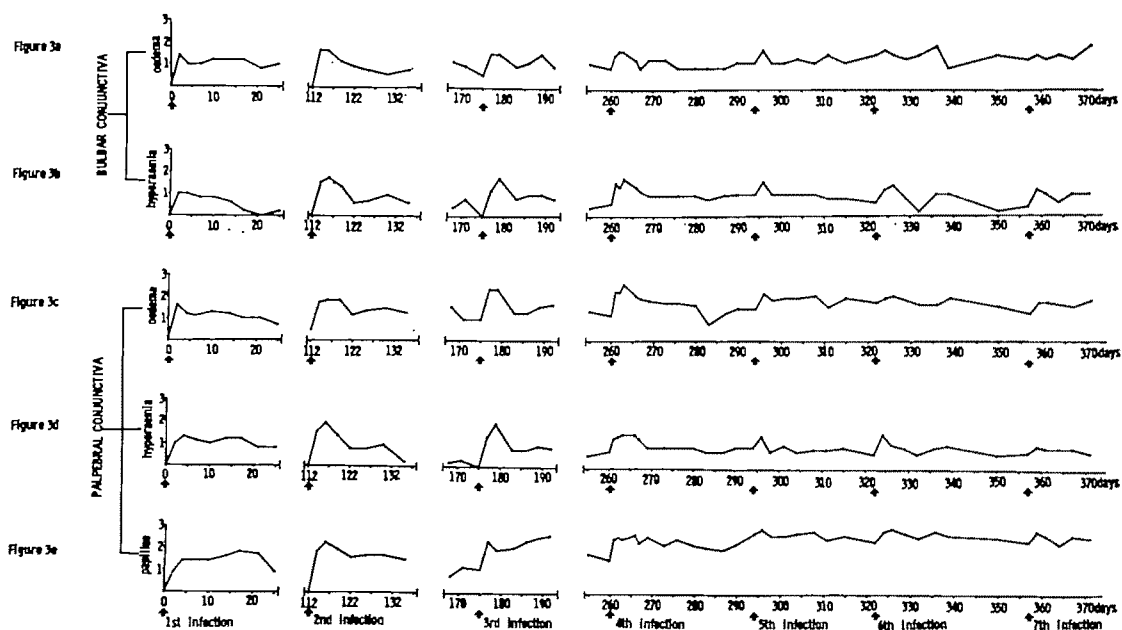


Fig. 3 The intensity and duration of signs in 5 animals to 7 successive GPIC infections. Arrows indicate inoculations.

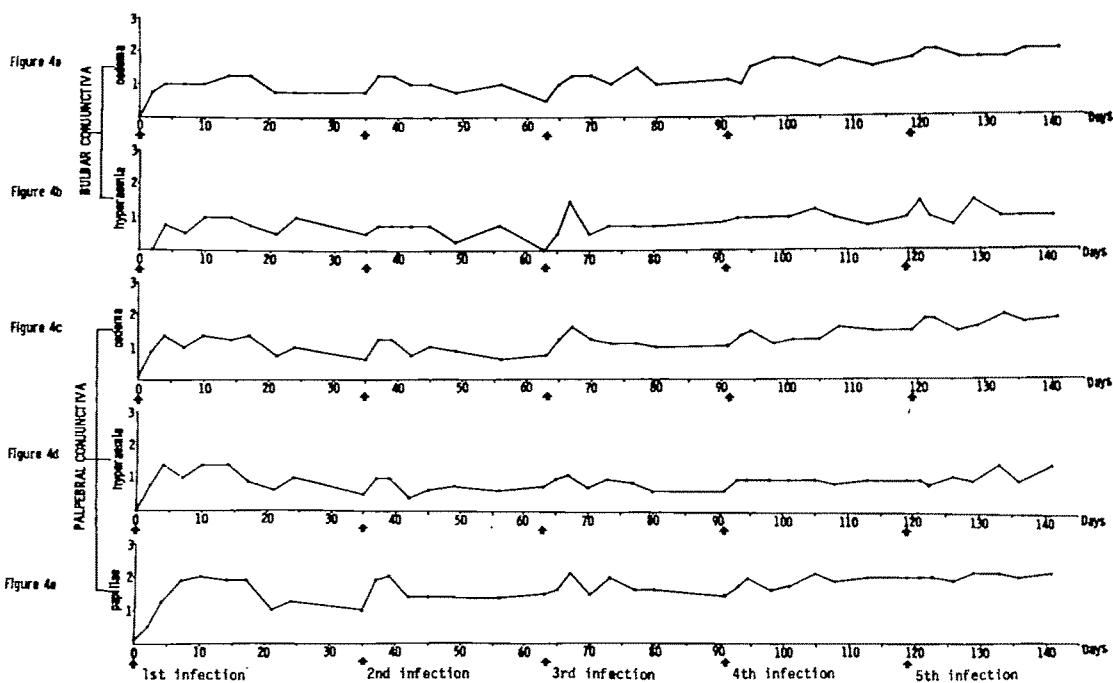


Fig. 4 The intensity and duration of signs in groups of 4 animals, which had not previously been scraped, to 5 successive GPIC agent infections. Arrows indicate inoculations.

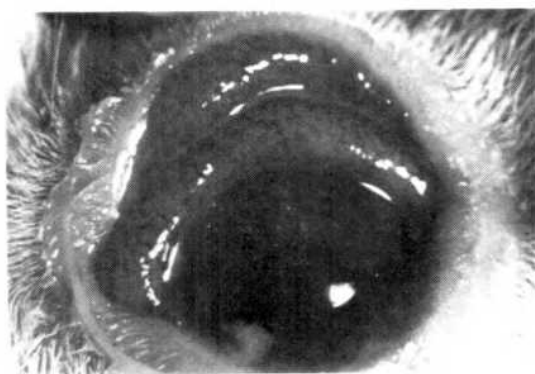


Fig. 5 Inflammatory responses 4 days after the second GPIC agent infection showing severe hyperaemia and oedema of the upper palpebral and bulbar conjunctivae.

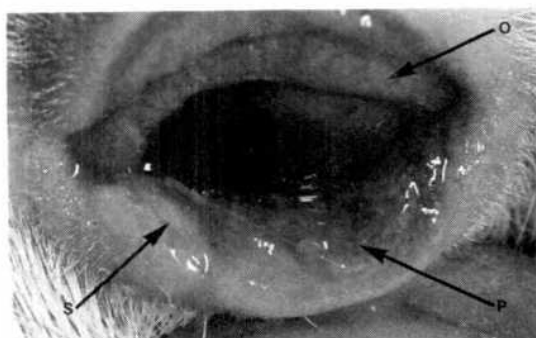


Fig. 6 Inflammatory responses 4 days after the seventh GPIC agent infection showing oedema of the bulbar (o), diffuse infiltration, severe papillary reaction (p) and scarring (s).

severity of the chronic inflammation resulting from previous infections was so great that very little, if any, increase was observed on subsequent inoculation.

SIGNS

The clinical signs were very similar in the 2 experiments. Lacrimation and discharge, and erythema and oedema of the lids were frequently observed for up to 7 days after reinfection but were rarely seen at other times.

The changes in the intensity of bulbar oedema and hyperaemia, palpebral oedema, hyperaemia, and papillae are shown in Figs. 3 and 4. Bulbar oedema tended to become progressively more severe in successive infections (Figs. 3a, 4a), particularly in the second experiment. Bulbar hyperaemia tended to be less severe, particularly in later infections (Figs. 3b, 4b, 5, 6).

In the palpebral conjunctivae the severity of hyperaemia, oedema, and papillary hypertrophy

were the same in upper and lower lids. The changes in the intensity of oedema and hyperaemia were similar to those seen in the bulbar conjunctiva (Figs. 3c, 3d, 4c, 4d, 5, 6). Papillary hypertrophy became more severe in successive infections (Figs. 3e, 4e).

No follicles were seen on the palpebral conjunctivae during primary infection, though the conjunctival folds, which became swollen during infection, looked similar to follicles. True follicles appeared during subsequent infections. A few small follicles were seen on both the upper and lower palpebral conjunctivae 7 to 10 days after the second infection; these soon disappeared. More follicles appeared during subsequent infections; these were larger and persisted for longer (Fig. 7). During later infections many large follicles were present on the upper palpebral conjunctiva, whereas progressively fewer and smaller follicles were found on the lower palpebral conjunctiva.

Small diffuse scars were observed on the lower palpebral conjunctiva of 3 animals used in the first



Fig. 7 The upper palpebral conjunctiva showing follicles.



Fig. 8 The lower palpebral conjunctiva showing diffuse scarring.

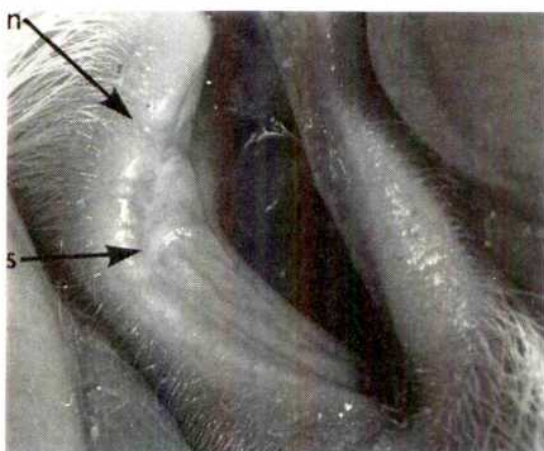


Fig. 9 The lower palpebral conjunctiva showing synechial scarring (s) and notch (n) at the lid margin.

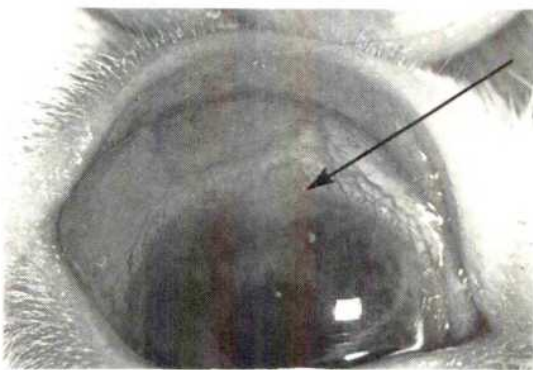


Fig. 10 Marginal diffuse keratitis.

experiment 65 days after the third infection. All 5 animals had developed diffuse scars 34 days after the fourth infection. The scarring became more severe during successive infections, and linear and synechial scars also developed (Figs. 8 and 9). In the second experiment, small diffuse scars were first seen on the lower palpebral conjunctivae of all 4 animals examined 4 days after the fourth infection. Larger diffuse scars were seen in animals during the fifth infection, and linear and synechial scars were occasionally seen.

In the cornea a mild diffuse epithelial and sub-epithelial keratitis was commonly observed for up to 7 days following the second infection (Fig. 10) and showed no increase in severity in successive infections. Neovascularisation associated with infiltration (active pannus) was detected in the upper region of the cornea. In the first experiment it was first observed 10 to 14 days after the fifth infection and was present in all 5 animals 3 months after the

seventh infection. In the second experiment it was first observed several weeks after the fifth infection (Figs. 11 and 12).

Deformities of the lower lids developed in 1 animal used in the first experiment. These were first observed several months after the seventh infection. A notch developed on the left lower lid which was associated with synechial scarring (Figs. 6 and 9), and entropion of the right lower lid, which was associated with heavy scarring (Figs. 8 and 13). In the second experiment entropion of the lower lid was observed in 6 eyes from 15 animals examined 12 months after the fifth infection. Deformities of the upper lid were not seen.

The right (uninoculated) eye also developed clinical signs of disease. These were similar to those seen in the inoculated eye, but were less severe, reaching a maximum 7 to 14 days after inoculation of the left eye. Chronic conjunctivitis, associated with follicles and scarring of the palpebral conjunctiva, and pannus also developed in the right eye.

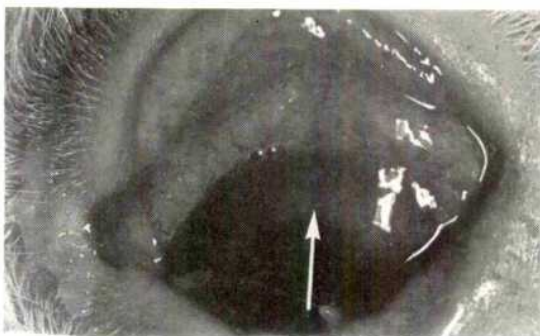


Fig. 11 Early pannus.

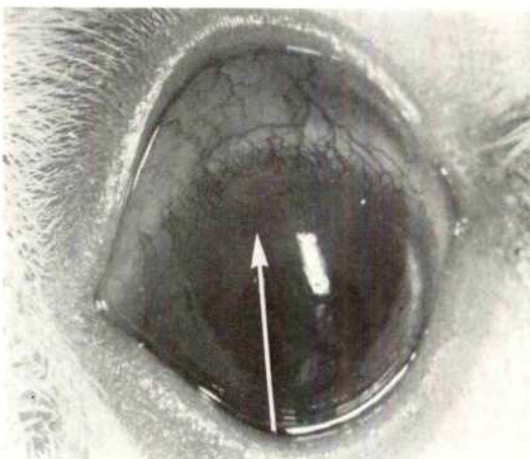


Fig. 12 Severe pannus with diffuse corneal infiltration.

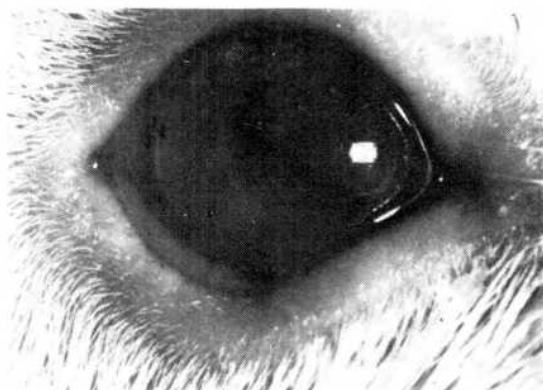


Fig. 13 Mild entropion of the lower lid associated with diffuse scarring (shown in Fig. 8).

CHLAMYDIAL INCLUSIONS

In both experiments, many inclusions were seen from days 2 to 21 after primary infection. The percentage of epithelial cells containing inclusions was greatly reduced in reinfection (Figs. 1*a* and 2*a*). In the first experiment inclusions were seen in scrapings from all 5 animals for up to 7 days after the second, third, and fourth infections, a few inclusions were seen in 2 out of 5 animals after the sixth infection; none were seen after the fifth and seventh infections (Fig. 1*a*). In the second experiment a few inclusions were seen in some animals 2 and 4 days after the second, third, and fourth infections; no inclusions were seen following the fifth infection (Fig. 2*a*).

POLYMORPHONUCLEAR CELLS

In the first experiment large numbers of polymorphonuclear cells were seen on days 2 to 17 following primary infection. In subsequent infections the number of cells was greatly reduced (Fig. 1*b*). In the second experiment far fewer cells were seen in the primary infection, and the numbers were further reduced in subsequent infections (Fig. 2*b*).

Most of the polymorphonuclear cells seen after reinfection were neutrophils, but a few eosinophils and basophils were also present.

MONONUCLEAR CELLS

In both experiments raised levels of mononuclear cells were seen from days 7 to 24 after primary infection (Figs. 1*c* and 2*c*). In the first experiment the number of cells seen in the 7 days following reinoculation was much higher except for the seventh infection. After the initial 7 days animals varied. Some had normal levels, and others had persistently raised levels of cells, so that no further increase was seen on reinoculation. No consistent pattern of

response followed the seventh infection (Fig. 1*c*).

In the second experiment raised levels of mononuclear cells were seen for 7 days after the second infection; after this some animals had high levels of mononuclear cells, and others had low levels. No consistent pattern of response was seen in the third, fourth, and fifth infections (Fig. 2*c*).

SERUM ANTIBODIES

Total serum antibodies against GPIC agent were measured in the animals used in the second experiment. Antibodies were first detected 10 days after primary infection and reached a peak on day 21. There was no significant change in the level of serum antibodies after 4 more infections (Fig. 2*d*).

Discussion

Repeated reinfection of guinea-pig eyes with GPIC agent produced chronic inflammation and lesions similar to those of trachoma. The microbiological and cytological responses to reinfection were very different from those seen in primary infection. Small numbers of inclusions were found for up to 7 days after reinfection and sometimes none were seen. This confirms previous observations that guinea-pigs became partially immune to GPIC agent after primary ocular infection.^{1,2,4,5} Similar observations have been made in owl monkeys and human volunteers infected with *Chlamydia trachomatis* strains isolated from patients with ophthalmia neonatorum or trachoma.^{6,7}

In our experiments the degree of immunity depended on the time interval between infections. When it was greater than 60 days, inclusions were seen in all animals for up to 7 days after reinfection (Fig. 1*a*). When it was reduced to 35 days or less, inclusions were only occasionally seen. Sometimes none were found (Figs. 1*a* and 2*a*). Fewer polymorphonuclear cells were seen during reinfection than in primary infection. They were found only when inclusions were present. Many more mononuclear cells were found than in primary infection. In the second infection of both experiments large numbers were present when inclusions were found, but in later infections high levels of mononuclear cells persisted for long periods when there were no inclusions. No increase in the levels of serum antibodies was seen after reinfection.

How is the reduction in the number of inclusions in reinfection mediated? A study of the role of humoral immunity has shown that in guinea-pigs the transfer of immune serum before primary ocular infection does not result in a reduction of the number of inclusions.⁸ Since we found increased numbers of mononuclear cells in the eye during reinfection, we

would suggest that they may mediate this reduction.

In guinea-pigs which have had an ocular GPIC agent infection a delayed-type hypersensitivity skin reaction is observed when live GPIC agent is administered intradermally,⁹ and we have observed large numbers of mononuclear cells at the sites of such skin reactions (unpublished results). Since ocular administration of live GPIC agent to previously infected animals produced severe inflammation accompanied by increased numbers of mononuclear cells, it seems reasonable to consider this reaction as an ocular delayed-type hypersensitivity reaction analogous to the skin reaction. Both the ocular and skin reactions could be elicited long after sensitisation—the skin reaction for at least 2 years after primary ocular infection⁹ and the eye reaction for at least 1 year after a previous ocular challenge. Uninfected yolk material did not produce dermal or ocular reactions (unpublished results).

Since chronic conjunctivitis developed in the animals used in both experiments, in the first of which animals were repeatedly scraped and in the second of which animals were used on 1 occasion only and scraped after clinical examination, we suggest that trauma plays little, if any, role in the production of chronic disease in guinea-pigs. Hanna¹⁰ found that, when American Indians with trachoma were subjected to two conjunctival scrapings at an interval of about 7 days, the number of inclusion-positive scrapings was significantly higher in the second set of specimens. We found inclusions in guinea-pigs with chronic conjunctivitis only within 7 days of reinfection, and repeated scraping did not increase the number of inclusions found in the 7-day period.

Experimental infection of humans with strains of *C. trachomatis* isolated from patients with trachoma, inclusion conjunctivitis, or ophthalmia neonatorum produced acute, self-limiting disease with no scarring or pannus. When a subject with previous exposure to *C. trachomatis* was reinoculated more severe disease resulted, with the development of pannus.¹¹

Wang and Grayston¹² found that in Taiwan monkeys infected with various strains of *C. trachomatis* primary ocular infection produced acute, self-limiting disease, and pannus developed only in animals with previous exposure to *C. trachomatis*.

Field studies in areas of Iran with a high prevalence of trachoma have shown that severe, active disease is common among children, who rarely have blinding complications. These complications are much commoner in adults, who rarely have active disease.¹³ Further studies by Darougar *et al.* (unpublished observations) have shown that mothers in large families with several young children have a higher incidence of both active disease and blinding

complications. These observations on naturally occurring disease show that the blinding lesions of trachoma are late events found when there is a high rate of reinfection.

Our guinea-pig experiments have shown that repeated reinfection produced severe delayed-type hypersensitivity reactions which were followed by the development of severe chronic disease and pannus, scarring, and lid deformities. We therefore suggest that in man the development of blinding hyperendemic trachoma is due to a high rate of reinfection combined with delayed-type hypersensitivity.

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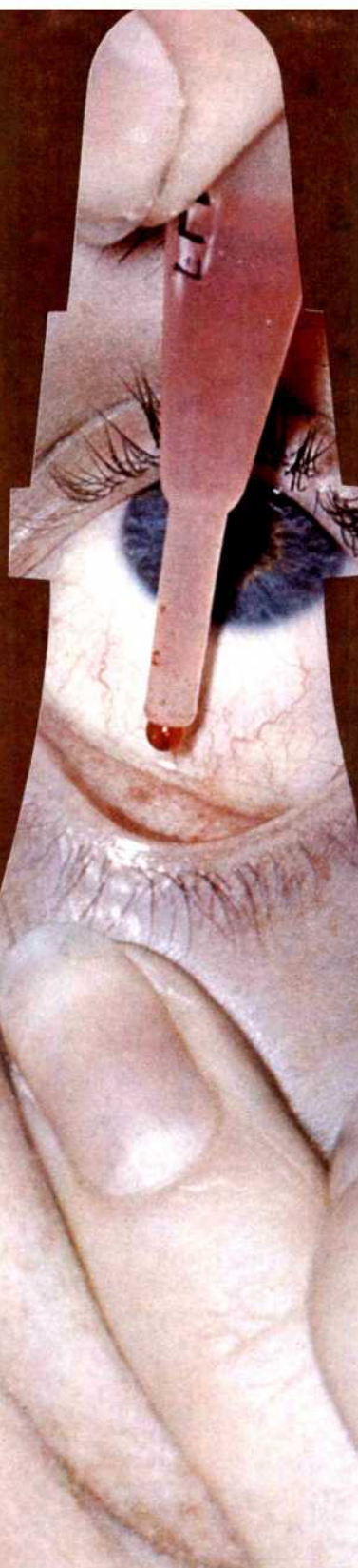
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Family-based suppressive intermittent therapy of hyperendemic trachoma with topical oxytetracycline or oral doxycycline

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SUMMARY A controlled double-blind stratified trial was carried out in a village in Southern Iran to assess the efficacy of family-based intermittent therapy of hyperendemic trachoma with topical oxytetracycline oily suspension twice daily for 7 days each month, or oral doxycycline 5 mg per kilogram of body weight once a month, in comparison with a control group which received vitamin pills once a month. In addition all other members of the selected children's families were also treated with the same regimen of therapy. The treatment was given for a period of 1 year by 3 field technicians, each responsible for one regimen of therapy. Examining the whole conjunctiva 4 months after the start of therapy, we observed no marked difference in the cure rate or the number of patients with moderate to severe trachoma between the groups treated with antibiotics and the control group. When treatment was continued for 12 months, a marked decrease in the prevalence of trachoma and in the grades of intensity of inflammatory responses as well as the positivity rate for *Chlamydia trachomatis* was observed in the groups treated with the topical oxytetracycline or oral doxycycline compared with the control group. While there was no marked difference between the efficacy of these 2 regimens of mass chemotherapy, the monthly intermittent therapy with a single dose of doxycycline offers the advantage of being more practical and less expensive for mass control of trachoma by requiring approximately one-tenth of the staff, transport, and other facilities required for the intermittent topical therapy with tetracycline eye ointment.

Intensive topical therapy with tetracycline or rifampicin is effective for hyperendemic trachoma.^{1,2} However, under field conditions the cost of delivery of such regimens of chemotherapy to the mass rural population is highly prohibitive. Alternatively, intermittent therapy with a topical tetracycline eye ointment twice daily for 5 to 7 days each month for a period of up to 6 months each year is recommended.³ Although this method of chemotherapy has been widely used, there is no evidence based on controlled studies to demonstrate its beneficial effects on preventing the blinding sequelae of trachoma by interfering with the transmission and reducing the severity of the disease.

Oral therapy with doxycycline is beneficial in the treatment of hyperendemic trachoma.⁴ In London treatment of patients suffering from paratrachoma (inclusion conjunctivitis and TRIC punctate keratoconjunctivitis) with a single dose of oral doxycycline 5 mg/kg body weight showed a marked clinical improvement for a period of up to 8 weeks and microbiologically a reduction of up to 50% in the *Chlamydia trachomatis* recovery rate (Darougar *et al.*, in preparation).

In this report we present the result of a controlled, double-blind, stratified trial which was designed to assess the efficacy of family-based intermittent therapy of hyperendemic trachoma with oxytetracycline oily suspension in comparison with intermittent oral therapy with doxycycline in a village in Southern Iran.

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Patients and methods

SELECTION OF PATIENTS

The total population of 450 in Sar-Rig, a village in the Bandar-Abbas area of southern Iran, was examined for signs of active trachoma.⁵ Patients with active trachoma in their whole conjunctiva were included in this study.

CLINICAL EXAMINATION

Eye examination was carried out with Haag-Streit slit-lamps. The signs observed in the whole conjunctiva, that is, upper tarsus and fornix and lower tarsus and fornix, were scored on a 0-3 scale and recorded separately for each area. The intensity of trachoma in the upper tarsus or the whole conjunctiva was calculated in accordance with the system described previously.²

LABORATORY INVESTIGATION

Conjunctival swabbings were collected from the whole conjunctiva of the right and left eyes.⁶ These were placed together in a plastic capsule containing 2SP transport medium⁷ with additional 3% fetal calf serum and stored in a liquid nitrogen refrigerator (-180°C) until transported to the laboratory in London. Here the specimens were stored in a -70°C refrigerator until the time of inoculation. The method of culture in irradiated McCoy cells and the identification of the isolates have been described elsewhere.⁸

RANDOM ALLOCATION

Patients with active trachoma were divided into 3 groups according to a randomisation schedule stratified for age, sex, intensity of trachoma, and the number of children with active trachoma in each family.

MEDICATION

Each group of patients was treated with one of the following 3 regimens of treatment. The first group received topical 1% oxytetracycline oily suspension twice daily for 7 days every month for 12 months. The second group received oral doxycycline 5 mg/kg body weight once a month for 12 months. The drug was given with a drink of milk to prevent vomiting. The control group received vitamin pills once a month for 12 months. All other members of the children's families, including parents, were also treated with the same regimen of treatment, but they were not included in this study. The treatment was given by 3 field technicians, each being responsible for one regimen of treatment.

FOLLOW-UP INVESTIGATIONS

After initial clinical and laboratory investigations

treatment was started. The follow-up clinical examinations with the collection of conjunctival swabbings were made 4 months and 12 months after the onset of treatment.

STATISTICS

Chi-square significance tests were used for the comparison of results.

Results

Initially 147 patients with active trachoma in their whole conjunctiva were included in this trial. Of these, 18 were excluded because of inadequate treatment or follow-up. The allocation of the 129 remaining patients to the 3 treatment groups and their ages and sex distribution are shown in Table 1.

Examining the whole conjunctiva 4 months after the start of treatment, we found no marked difference in the cure rate or the number of patients with moderate to severe trachoma between the groups treated with topical oxytetracycline or doxycycline and the control group (Fig. 1). However, after 12 months of treatment the cure rates in the groups treated with oxytetracycline or doxycycline were 50% and 45% respectively compared with 28% in the control group (Table 2, Fig. 1). The difference between the results of treatment with the antibiotics compared with the control group reaches statistical significance at a level of $P < 0.05$. The difference between the efficacy of the 2 antibiotics was not statistically significant. There was also a marked reduction in the intensity of trachomatous inflammatory responses in the patients who were not cured. The percentage of patients with moderate to severe trachoma was reduced from 70% to 49% for the control group compared with a reduction from 84% to 21% for oxytetracycline and from 77% to 25% for doxycycline (Table 2, Fig. 1).

The changes in trachomatous inflammatory responses observed in the upper tarsal area alone in groups treated with topical oxytetracycline or oral doxycycline in comparison to the control groups are shown in Table 3 and Fig. 2. In general the response to treatment after 4 months and 12 months

Table 1 Allocation of patients to various treatments and their age and sex distribution

Treatment	No. of patients	Age				M/F (ratio)
		0-1	2-4	5-9	10-11	
Control	47	2	21	17	7	20/27
Oxytetracycline	38	4	15	10	9	12/26
Doxycycline	44	4	11	21	8	20/24

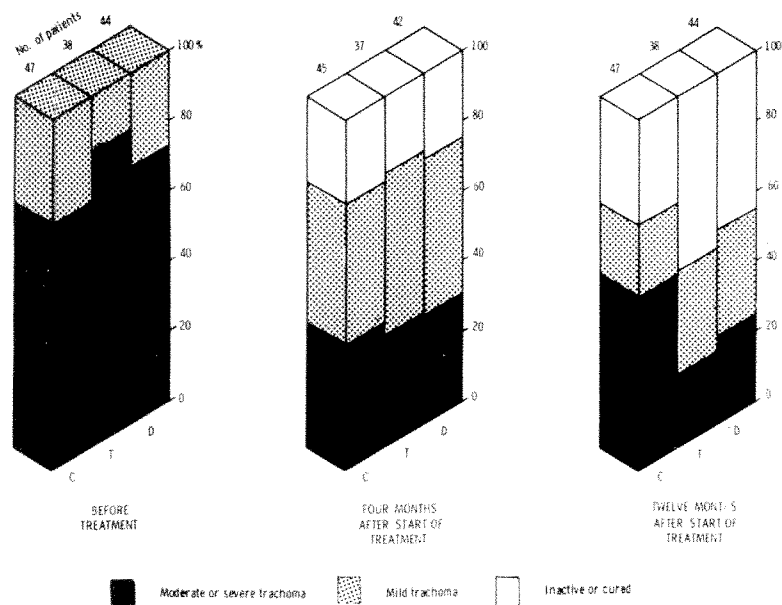


Fig. 1 Changes in the grades of intensity of trachoma in the whole conjunctiva after intermittent therapy with topical oxytetracycline oily suspension (T), oral doxycycline (D), and placebo (C).

Table 2 Changes in grades of intensity of trachomatous inflammatory responses in the whole conjunctiva following 12 months of intermittent treatment with topical oxytetracycline, oral doxycycline, or placebo

Type of treatment	No. of patients	Number of patients with different grades of intensity*					
		Before treatment			After treatment		
		0-1	2	3-4	0-1	2	3-4
Placebo	47	0	14 (30%)	33 (70%)	14 (28%)	10 (23%)	23 (49%)
Oxytetracycline	38	0	6 (16%)	32 (84%)	19 (50%)	11 (29%)	8 (21%)
Doxycycline	44	0	10 (23%)	34 (77%)	20 (45%)	13 (30%)	11 (25%)

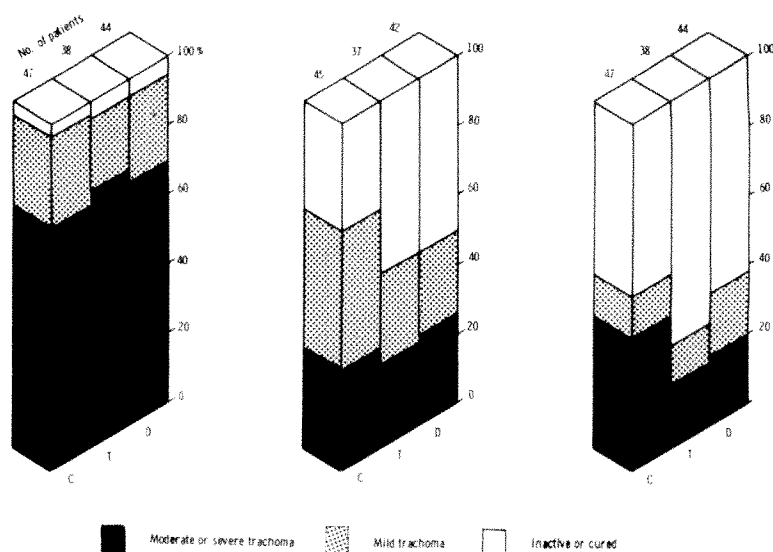
*0-1 = Inactive, 2 = Mild, 3-4 = Moderate to severe.

Table 3 Changes in grades of intensity of trachomatous inflammatory responses in the upper tarsal conjunctiva following 12 months of intermittent treatment with topical oxytetracycline, oral doxycycline, or placebo

Type of treatment	No. of patients	Number of patients with different grades of intensity*					
		Before treatment			After treatment		
		0-1	2	3-4	0-1	2	3-4
Placebo	47	2 (4%)	12 (26%)	33 (70%)	21 (45%)	8 (17%)	18 (38%)
Oxytetracycline	38	2 (5%)	8 (21%)	28 (74%)	27 (71%)	4 (11%)	7 (18%)
Doxycycline	44	2 (5%)	11 (25%)	31 (70%)	27 (61%)	8 (19%)	9 (20%)

*0-1 = Inactive, 2 = Mild, 3-4 = Moderate to severe.

Fig. 2 Changes in the grades of intensity of trachoma in the upper tarsal conjunctiva after intermittent therapy with topical oxytetracycline oily suspension (T), oral doxycycline (D), and placebo (C).



with either of the antibiotics was more apparent in the upper tarsal conjunctiva than in the whole conjunctiva (Figs. 1 and 2).

Microbiologically 47% of patients allocated to the control group were positive for *Chlamydia trachomatis* before treatment compared with 26% and 36% of patients in the topical oxytetracycline or oral doxycycline groups respectively. Follow-up tests 4 months after the start of treatment showed a marked decrease in the positivity rate for *C. trachomatis* in the group treated with topical oxytetracycline (Table 4). After 12 months of treatment the positivity rate for *C. trachomatis* in the groups treated with oxytetracycline or doxycycline was 3% and 7% respectively compared with 19% in the control group. The difference in the rates of positivity for *C. trachomatis* between the treated groups and the control group is significant at a level of $P < 0.05$. The difference between the positivity rates following the treatment with the 2 antibiotics for 12 months was not statistically significant.

Table 4 Number of positive cultures for *C. trachomatis* before and after chemotherapy

Type of Treatment	No. of patients	No. of positive cultures		
		Before treatment	After treatment	
			4 months	12 months
Placebo	47	22 (47%)	7 (16%)	9 (19%)
Oxytetracycline	38	10 (26%)	1 (3%)	1 (3%)
Doxycycline	44	16 (36%)	7 (17%)	3 (7%)

Discussion

In this trial preschool and school children with active trachoma were included. Stratified randomisation for age, sex, and grades of intensity of trachomatous inflammatory responses produced a well balanced distribution of patients in the groups allocated to the active and placebo treatments (Tables 1 and 2, Figs. 1 and 2). Microbiologically, before treatment the number of patients positive for *C. trachomatis* was lower in the group allocated to the topical oxytetracycline than in the other 2 groups (Table 4).

During the follow-up studies of the control group we found a considerable degree of natural decline in the prevalence of trachoma, in the intensity of inflammatory responses, and in the positivity rate for *C. trachomatis* (Tables 2, 3, and 4, Figs. 1 and 2). The degree of natural decline of trachoma in our control group was much higher than that observed in Tunisia.¹ Apart from the effect of increasing age this could be attributed in part to the reduction in the level of interfamily transmission in the village following therapy with antibiotics of the majority of the cases of active trachoma (reservoirs of infection) included in the other 2 groups and to the steady improvement of socioeconomic conditions in the village.

This study showed that a 4-month course of intermittent therapy with either topical oxytetracycline or oral doxycycline is not sufficient to reduce the intensity of trachomatous inflammatory responses in the conjunctiva. But when the treatment

was continued for 12 months a marked decrease in the prevalence of trachoma and in the grades of intensity of inflammatory responses as well as the positivity rate for *C. trachomatis* was observed (Figs. 1 and 2).

Assessing the inflammatory changes of trachoma in the upper tarsal conjunctiva alone, we found the cure rate for all 3 groups was approximately 30% higher than that obtained by examining the whole conjunctiva (Tables 2 and 3, Figs. 1 and 2). This finding confirms our previous observation that active but mild to moderate trachomatous inflammatory changes may persist in the upper fornix and the lower lid conjunctivae of some of the patients with cured upper tarsal conjunctiva. This residual inflammation in the upper fornix and the lower lid is shown to be related to the increased risk of recurrence of moderate and severe trachoma in the whole conjunctiva, including the upper tarsal area.³

In assessing the result of this trial we may conclude that intermittent therapy with topical oxytetracycline or oral doxycycline are both effective against trachoma clinically and microbiologically if they are used for a period of 1 year. While no marked difference was observed between the efficacy of these 2 regimens of mass chemotherapy, the monthly intermittent therapy with a single dose of doxycycline offers the advantage of being more practical and less expensive for mass control of trachoma by requiring approximately one-tenth of the staff, transport, and other facilities needed for the intermittent topical therapy with tetracycline eye ointment.

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A modified technique for correction of trichomatous cicatricial entropion*

C. P. THOMMY

From the Guinness Ophthalmic Unit, Ahmadu Bello University Teaching Hospital, Kaduna, Nigeria

SUMMARY Cicatricial entropion resulting from trachoma occurs in various grades of severity. No one technique of surgical correction is suitable for all types. The technique has to be modified in accordance with the severity of the condition. A modified technique using skin graft is described, and excellent results (93.8%) in 380 lid corrections with minimal recurrences during a follow-up period of over 2 years are presented.

Entropion and trichiasis present in various grades of severity in areas where trachoma is endemic. No one method is suitable for surgical correction of these various grades of severity. This is why there are innumerable methods and modifications for entropion correction. A mild entropion may be corrected by a simple skin muscle excision, whereas a severely scarred lid calls for more radical methods with a combination of techniques. The choice of technique thus depends on the severity of entropion. Some of the available techniques are simple, others have more involved procedures, and some have certain drawbacks (Hadija, 1960) with consequent corneal changes. Some give higher success rates than others, depending on the aetiology and severity of entropion (Bercovici *et al.*, 1977).

This paper presents a modified method for correcting extensive cicatricial entropion and trichiasis which is simple, has fewer drawbacks, and is followed by fewer recurrences.

Material and methods

380 eyes (360 bilateral, 20 unilateral) of 200 patients, predominantly female (170 females, 30 males) between the ages of 5 and 80 years (largest number between 15 and 56 years) were operated on for severe entropion/trichiasis resulting from trichomatous scarring. The operations were done at the Guinness Ophthalmic Unit of Ahmadu Bello Uni-

versity Teaching Hospital, Kaduna, Nigeria, from October 1976 to January 1979. 178 patients (341 eyes—326 bilaterally corrected and 15 unilaterally) were observed for a minimum period of 4 months and a maximum of 2 years and 4 months, 70% having been seen over 1½ years.

Technique

Under local infiltration anaesthesia for adults and general anaesthesia for children the lid is split intermarginally for its whole length with a No. 15 Bard Parker knife; a lid guard stretches the lid and protects the eyeball. The depth of the split depends on the mobilisation needed of the cilia-bearing flap, which in turn depends on the severity of entropion and trichiasis. The cilia roots, if any, on the posterior flap are excised completely. If the tarsal plate is very thickened and/or infected, it is sufficiently excised. At both ends, just beyond the last cilia, the incision is continued upwards for about 3 to 4 mm, dividing the pretarsal orbicularis fibres and the anterior fibres of the muscle of Riolan. At the medial end care is taken to avoid the punctum (Fig. 1). Two parallel skin incisions are now made horizontally about 1.5 to 2 mm apart, the first being 3 to 4 mm above the lid margin and joining the 2 vertical cuts. This strip of skin is dissected free but not severed at either end, and brought down below the anterior flap, the attached ends passing through the vertical cuts (Fig. 2). A polyethylene tube is placed over this graft, and 4 to 5 mattress sutures with 4/0 silk are taken to include the skin incisions, the graft, and the polyethylene tube. Care is taken to pass the sutures through the

*This paper was presented in part at the 13th International Congress of Ophthalmology, Kyoto, Japan, 14–20 May 1978.

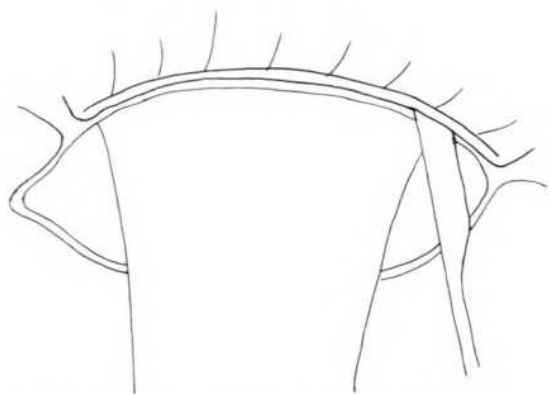


Fig. 1 The lid is split intermarginally and at each end continued upwards for 3-4 mm

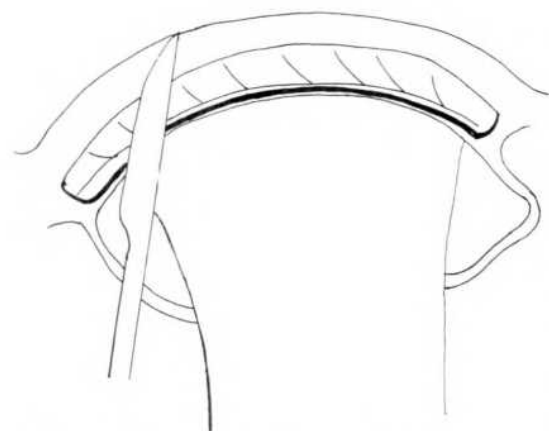


Fig. 2 The skin graft is dissected, the first incision joining the vertical cuts

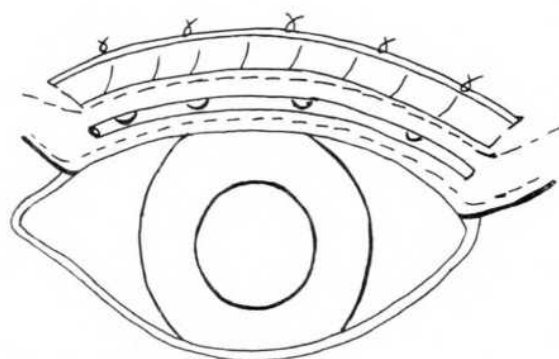


Fig. 3 The skin graft is sutured in the intermarginal space under a polyethylene tube, the unserved ends passing through the vertical cuts



Fig. 4 The corrected eye

lower margin of the graft, and they are tied with optimum tension above the upper skin incision (Fig. 3).

Particular care is taken to excise completely all cilia roots from the posterior flap; to include the very last lash at both ends within the upward cuts; to have the graft lie properly in upward cuts at both ends; to pass sutures through the lower border of skin graft; and to leave about 2 mm of free edge of the posterior flap.

A pad and bandage is applied. Daily dressing is done for 3 days, after which dressing is discarded. Sutures and tube are removed on 7th or 8th day.

Results

320 corrections out of 341, followed up (93.8%) were well maintained during the period of observation. There were no significant complications during or after surgery. There were no recurrences of entropion, but in a few cases (21=6.6%) a few misdirected lashes were seen to be growing from the lower flap, which were promptly removed by electrolysis.

Subjective improvement of wellbeing, with absence of irritation, blepharospasm, photophobia, watering, discharge, and a gradual clearing of the cornea, were remarkable, as might be expected (Fig. 4).

Discussion

Extreme severity of trachomatous scarring calls for radical techniques and a combination of procedures for surgical correction (Callahan and Dortzbach, 1970), because these cases are often complicated by long-standing neglect, indigenous surgery and medication, and repeated attempts at correction. Some of these cases are amenable to tarsotomies (Hadija, 1960), including modifications of Weis's (Ballen, 1964; Sandford-Smith, 1976) or

to tarsectomies (Boase, 1952; Jones *et al.*, 1976). Grafting of split intermarginal strip with mucous membrane, with modifications (Spaeth, 1948) of Van Milligan's technique (Callahan and Dortzbach, 1970) or with skin by the modification by King and Wadsworth (1970) of Macheck-Blaskovic's technique are suitable in other cases.

The author further modifies the skin graft technique by making vertical cuts at both ends of the lids, also partially severing the pretarsal and Riolan's fibres. This procedure has the following advantages. Firstly, it facilitates better and easier mobilisation of the anterior cilia-bearing flap. Secondly, the descending attached portions of the skin graft at both ends can be perfectly placed in these cuts. This procedure prevents the formation of cysts and fistulae, gives a fine cosmetic result, bridges the gap between the cut ends of the pretarsal and anterior fibres of Riolan, removes the element of blepharospasm from the link of the vicious circle in the production and maintenance of entropion, helps healing during the immediate postoperative period, and maintains the correction later, preventing recurrence. It is also possible that it prevents the sliding of the preseptal orbicularis fibres over the pretarsal fibres (Jones and Wobing, 1976).

There was no recurrence of entropion in this series, so that the mechanical correction of entropion is fully successful. The 6.6% recurrence of trichiasis was because of nonexcision of all the cilia roots from the lower flap from where the misdirected lashes grew. This can therefore be prevented by complete excision of all the lash roots on the lower flap. Paring away of thickened and/or infected tarsal tissue leaves the desired thickness of the tarsus throughout its length for a nearly normal lid structure without any chance of vertical shortening of the lid.

The intention is always to make the intermarginal incision above the orifices of the Meibomian glands, but it is often difficult to carry out because of the altered anatomy of a scarred lid both from disease and previous treatment. However, no deleterious effect was seen on the cornea because of any possible alteration in the precorneal film.

The favourable results, absence of complications, and minimal recurrences of trichiasis may be attributed to the following factors: the vertical incisions severing the pretarsal and Riolan's fibres; better mobilisation of the anterior flap; the skin graft maintaining the correction; the use of a polyethylene tube for optimum positioning of the graft and the everted position of the cilia-bearing layer; the excision of the scarred tarsal plate and removal of all cilia roots from the lower flap; the mattress sutures along with the polyethylene tube

enhancing the correction and maintaining it during the healing period; and the 'pedicled at both ends' skin graft, which always takes.

The method is simple, in that the graft is from the same lid. The polyethylene tube is readily available (it is smooth and pliable and cosmetically acceptable during the postoperative period). The procedure is short (average time 7 minutes), and it can be performed anywhere, usually as an outpatient procedure.

The only possible drawback to this procedure is the presence of minute downy hairs on the graft. This is prevented from rubbing the cornea by the anterior placement of the graft, taking the sutures at the lower border of the graft, suturing it to the anterior cilia-bearing layer, and leaving about 2 mm of free margin of the lower posterior flap.

The results are encouraging (93.8%), and, if particular attention is paid to the details of the procedure, recurrences may be entirely avoided and the downy hairs prevented from rubbing on the cornea. Functionally it is satisfactory. Cosmetically, the method is excellent, the postoperative appearance being most natural. There is no staring, no entropion, and no vertical shortening of the lid.

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Book reviews

Ophthalmic Plastic Surgery for the General Ophthalmologist. By MURRAY A. MELTZER. Pp. 84. \$20.75. Williams and Wilkins: Baltimore, Maryland. 1979.

This book is written for the general ophthalmologist, as its title suggests. It aims to provide him with a practical guide to basic ophthalmic plastic surgical procedures and in no way attempts to cover the subject comprehensively. The procedures are well described and illustrated with good line diagrams. Almost the whole of the first half of the book is devoted to anatomy and basic principles. Too little space is left for an adequate discussion of the indications and contraindications for specific operations and of the management of complications. This particularly affects the chapter on blepharoptosis. It would, however, be impossible to cover all aspects of the subject in a book of this size, and the author is to be congratulated on producing such a complete guide without increasing the text. It should be of value, as intended, to general ophthalmologists who want a summary of some of the simple practical eyelid procedures which they are frequently required to do. J. R. O. COLLIN

Documenta Ophthalmologica Proceedings. Electrodiagnosis, Toxic Agents, and Vision. 15th I.S.C.E.V. Symposium, Ghent, 1977. Vol. 15. Ed. J. François and A. De Rouck. Pp. 343. \$56.00. Junk: The Hague. 1978.

This book is a compilation of the proceedings of the 15th meeting of the International Society for Clinical Electrophysiology. The name of the society has been changed recently to allow it to embrace work on cortical evoked potentials and it now bears the initial letters ISCEV. Although these papers were actually given in 1977, the book contains some useful information for both clinicians and laboratory workers.

The first part is concerned with the effect of drugs on the electrical responses, and there is some much needed information on the effect of anaesthetics. A rather horrifying report of a case of chloroquine ocular toxicity in a patient on an antimalarial dosage is backed up by others on the progressive nature of chloroquine damage even after cessation of treatment. Further papers were presented on the details of the waveform of the ERG, EOG, and VER. In particular a clear-cut comparison is given between the VER produced by square wave and sinusoidal checkerboard stimuli. On a more clinical level there is a large series of results demonstrating the place of the VER in the assessment of patients with cataracts, and for those interested in questions of health and safety there is a well documented measurement of the retinal damage threshold to visible light. At the end of the book there are some short papers on instrumentation, including a description of the now well known gold-coated Mylar electrode for use in electroretinography.

In the past the proceedings of ISCEV have probably not been read widely enough by clinical ophthalmologists and indeed have been difficult to obtain. The papers in Volume 15 deserve to attract some interest and will provide a useful reference source. N. R. GALLOWAY

Perinatal Retinal Haemorrhages: Morphology, Aetiology and Significance. By B. VON BARSEWISCH. Pp. 184. DM58. Springer-Verlag: Berlin. 1979.

The fascination for the interesting subject of this book that the author has felt for some years comes over clearly in his carefully prepared monograph. After describing the morphology of these haemorrhages, with clinicopathological correlation, he discusses the aetiological factors in some detail and then turns his attention to the significance of the findings. Evidence is produced in the form of excellent serial fundus photographs. Retinal haemorrhages occur in about one-third of all deliveries, being more frequent when the second stage of labour has been complicated, and they are not influenced by maturity, sex, parity, or blood coagulation disorders. At the macula the commonest haemorrhage is submembranaceous (under the internal limiting membrane), and this almost invariably leaves no functional sequelae and is not necessarily associated with intracerebral haemorrhage.

Although many readers may regard this as an obscure subject, the very frequency of perinatal retinal haemorrhages and the thorough way in which this monograph has been prepared will certainly lead to this book's taking its place in the established ophthalmic literature.

DAVID TAYLOR

Chronic Progressive External Ophthalmoplegia. By L. A. K. BASTIAENSEN. Pp. 385. No price given. Stafleu's Scientific Publishing Company: Leyden. 1978.

This 400-page book provides a modern review of a condition ophthalmologists will rarely see but in which their observations historically have been, and clinically continue to be, of immense value. It was first described by an ophthalmologist, von Graefe, and attributed to a muscle disorder by two neurologists, Kiloh and Nevin, but it remained for Dr Kearns of the Mayo Clinic to indicate the protean manifestations with pigmentary retinopathy and cardiac conduction defects. Over the last decade histologists and electron microscopists have established subtle abnormalities in mitochondria, and the breadth of the clinical spectrum has been extended. This compilation is orientated around the author's work but contains an excellent bibliography and review of a wide range of conditions that may produce ophthalmoplegia. M. D. SANDERS

Correspondence

Appeal for necropsy material from human amblyopes for morphological study

SIR, Basic research in the medical sciences does not always seem to have direct consequences for the clinician. However, sometimes the relationships may be close. One area in which this may be true is the study of experimental amblyopia.

Since the work of Wiesel and Hubel in 1963 it is known that there are easily detectable and measurable morphological changes in the lateral geniculate nuclei of animals deprived of normal vision in their early postnatal life. Since then much work has been devoted to the study of the changes in the visual cortex and the lateral geniculate nucleus after visual deprivation by lid suture, experimental strabismus, or anisometropia, changes that are probably similar to those underlying amblyopia in man. From this work have come many basic concepts of direct clinical relevance, such as the very short time of visual deprivation necessary in the early weeks of life that cause severe central nervous changes, and the importance of early intervention if the situation is to be rectified.

We have been involved, along with many others, in research in experimental amblyopia, particularly in the monkey, which is probably the animal most comparable to man. We are struck that, to our knowledge, no case of human amblyopia has been studied post mortem using the techniques available to the experimental scientist. If we are to correlate animal results with possible clinical consequences it is vital to try to pursue such a study.

What is needed is collaboration between the ophthalmologist, the pathologist, and the basic scientist to obtain specimens from the brains of human amblyopes. One reason that this has been so difficult to accomplish in the past is that amblyopia is not a fatal disease. The chances are that the amblyope will die under circumstances totally unrelated to ophthalmological problems. Even if a necropsy is performed, the old eye pathology is likely to be forgotten. However, if ophthalmologists could be made aware of the need to obtain brain tissue from amblyopes, even years after the end of their treatment, perhaps our aim could be fulfilled.

We therefore appeal to the ophthalmologist to notify the pathologist if one of his amblyopic patients should come to necropsy, and to the pathologist to try to ascertain whether cases he sees have a history of amblyopia. Of particular interest, in addition to cases of strabismic amblyopia, would be brain specimens from patients with ocular occlusion with an onset during infancy, such as caused by congenital or infantile cataracts, tumours of the lids, corneal opacification, or any other cause. If such material were to become available, simple fixation of the posterior thalamus including the lateral geniculate nuclei and of the occipital lobes including the visual cortex in 10% formalin would suffice for our purposes.

If you can help, please contact one of the undersigned, who will be happy to give you more details of this project.

LAURENCE J. GAREY,
Institute of Anatomy,
Rue du Bugnon 9,
1011 Lausanne,
Switzerland.
(Tel. (021) 23 22 62.)

GUNTER K. VON NOORDEN,
Baylor College of Medicine,
Department of Ophthalmology,
Texas Children's Hospital,
PO Box 20269,
Houston, Texas 77025, USA.
(Tel. (713) 791-3183.)

Notes

International Optometric and Optical League

The 53rd congress of the IOOL will be held in Nagoya, Japan, on 26-30 May 1980. Details from the Secretariat, c/o Simul International Inc., Kowa Building No. 9, 1-8-10, Akasaka, Minato-ku, Tokyo 107, Japan.

Glaucoma up to date

The annual conference of the Glaucoma Service of the Wills Eye Hospital will be held on 6-7 June 1980. Further details from Dr K. Benjamin, c/o Glaucoma Service, Wills Eye Hospital, 1601 Spring Garden Street, Philadelphia, Pa 19130, USA.

Canadian Ophthalmological Society

The 43rd Annual Meeting will be held in Vancouver, British Columbia, Canada, on 8-11 June 1980 at the Hotel Vancouver. The principal speakers will be Dr Donald Gass, Miami; Dr Alston Callahan, Birmingham, Alabama; Professor Barrie Jones, London; and Dr Andrea Cibis-Tongue, Portland, Oregon. Details from PO Box 8844, Ottawa, Ontario, Canada K1G 3G2.

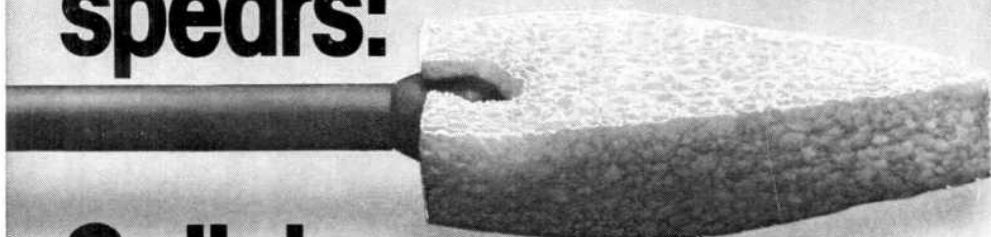
International Society for Contact Lens Research

The first scientific meeting of this society will be held at the Royal College of Surgeons, London, on 5-6 September 1980. All who have an interest in research and wish to attend or participate should write as soon as possible to Mr Montague Ruben, Moorfields Contact Lens Department, Cayton Street, London EC1. Details of membership can be obtained at the same time.

Lens implants

The United Kingdom Intraocular Implant Society will hold its autumn meeting at the Manor House Hotel, Moretonhampstead, Devon, on 1-3 October 1980. It will include the Rayner lecture and video demonstrations of lens implantation. Details from Mr W. J. Rich, West of England Eye Infirmary, Magdalen Street, Exeter.

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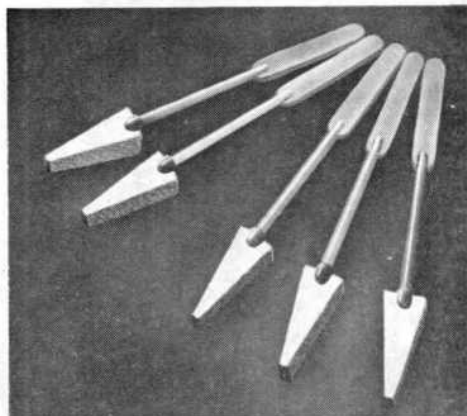


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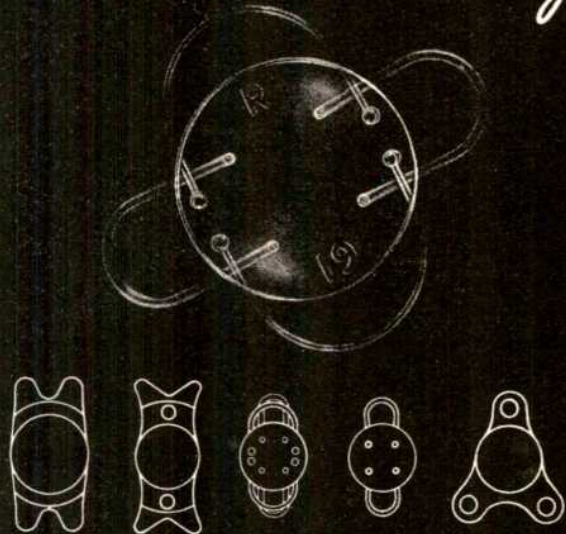
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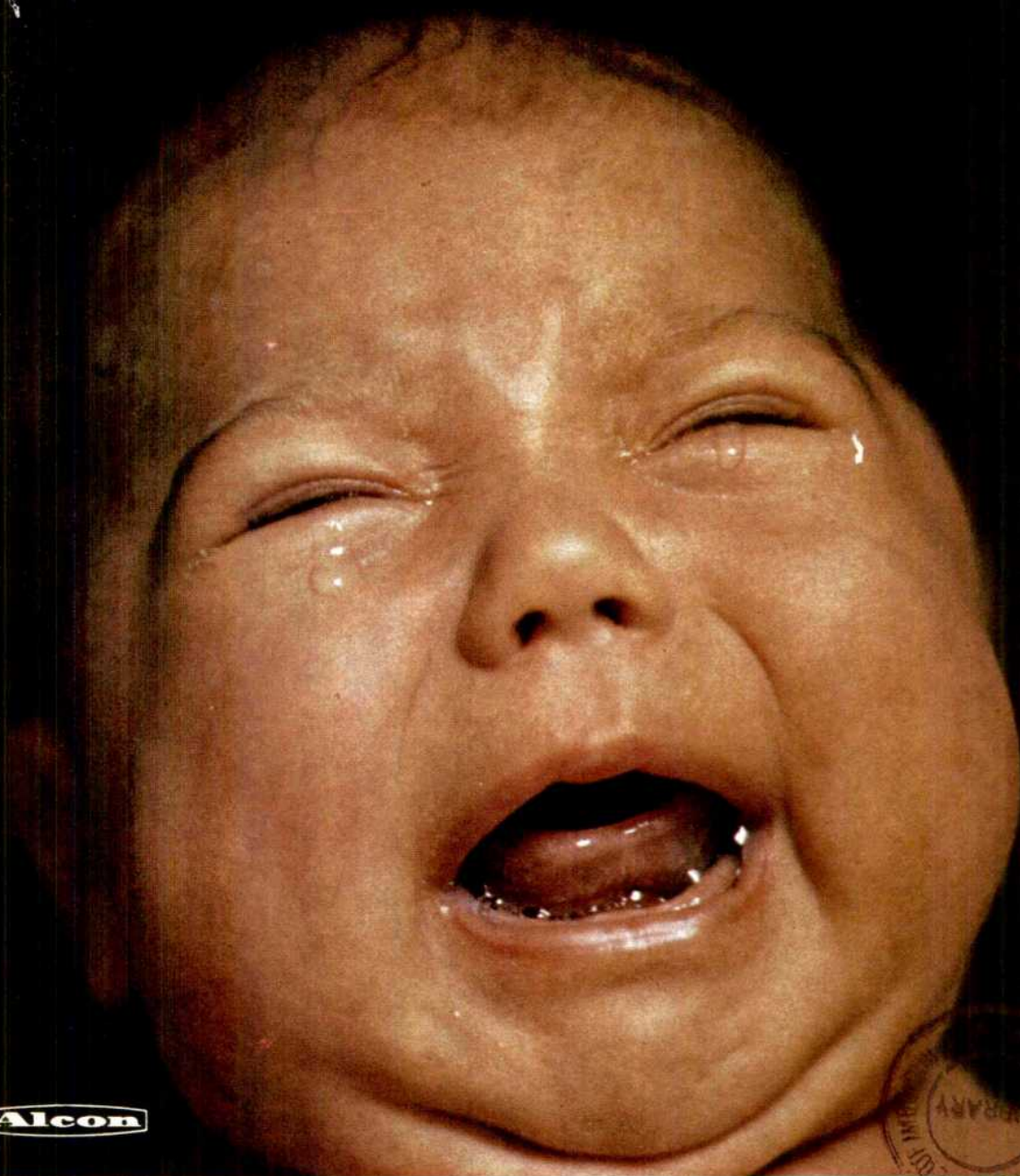
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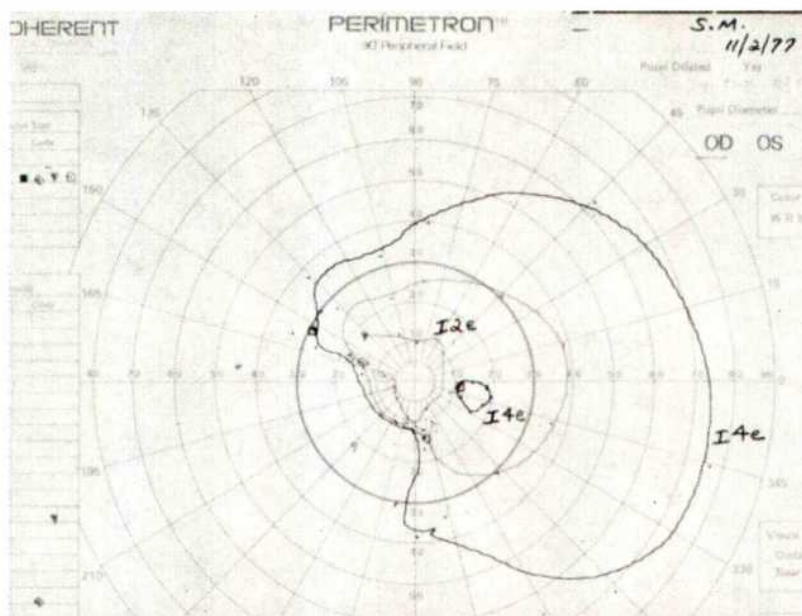


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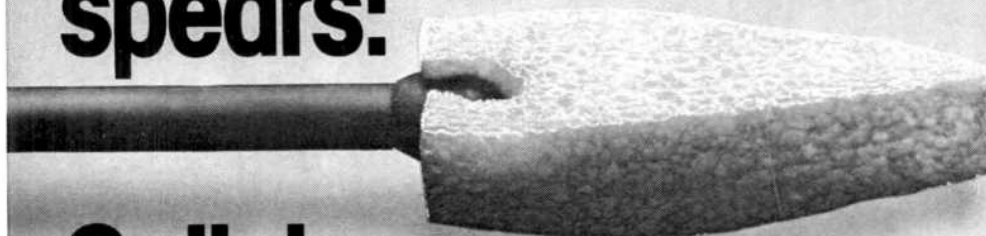
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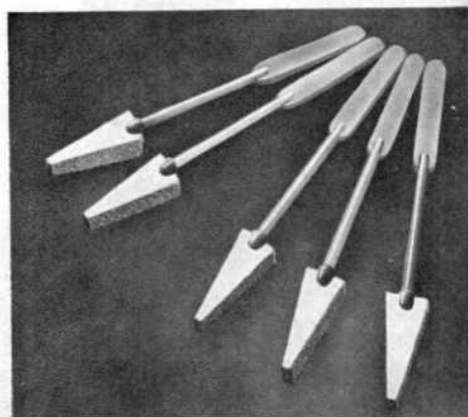


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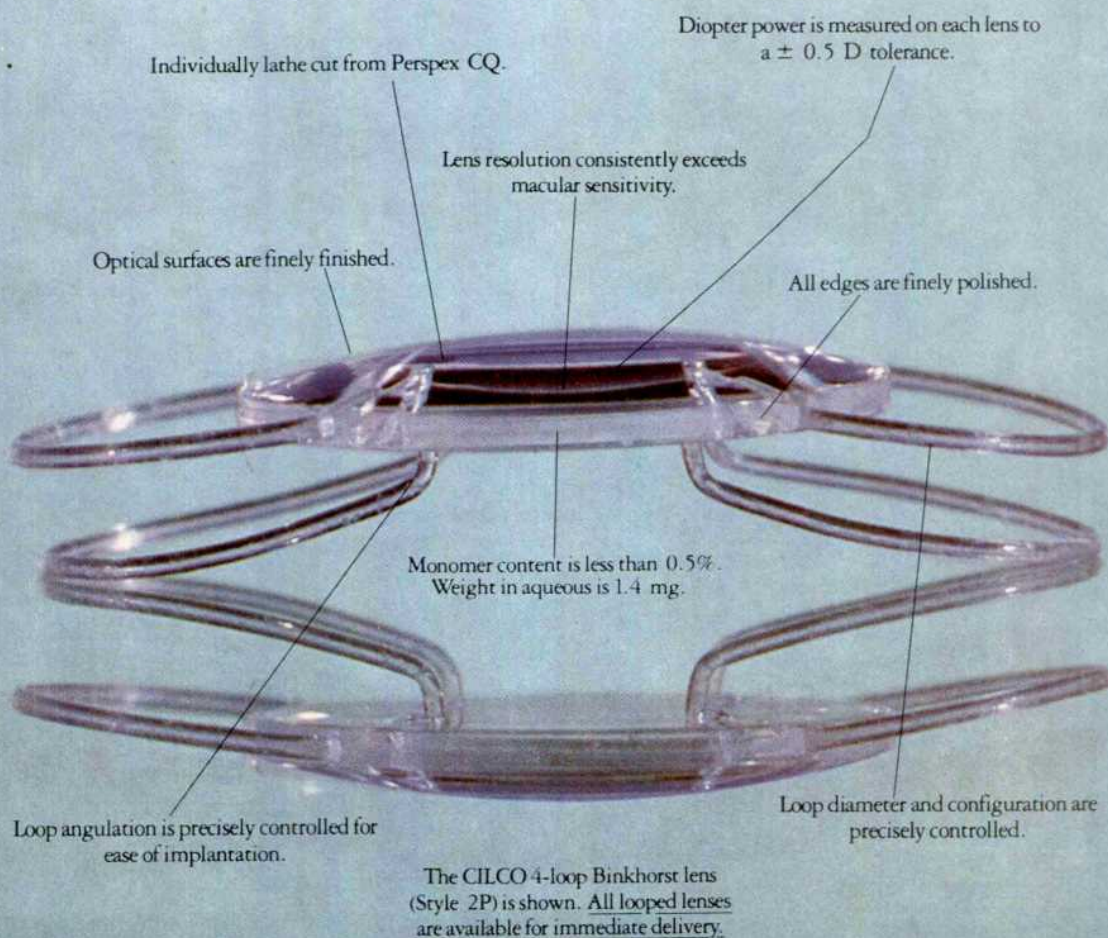
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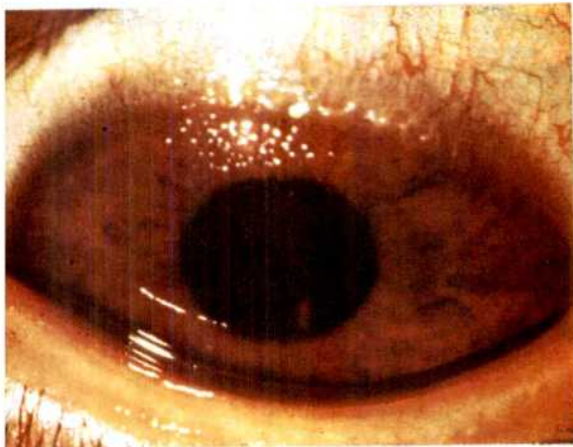
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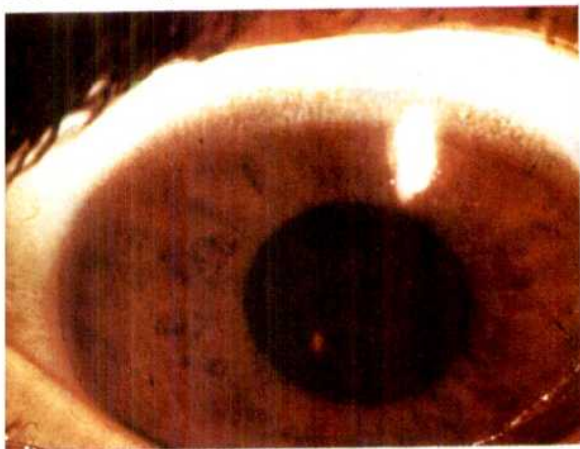
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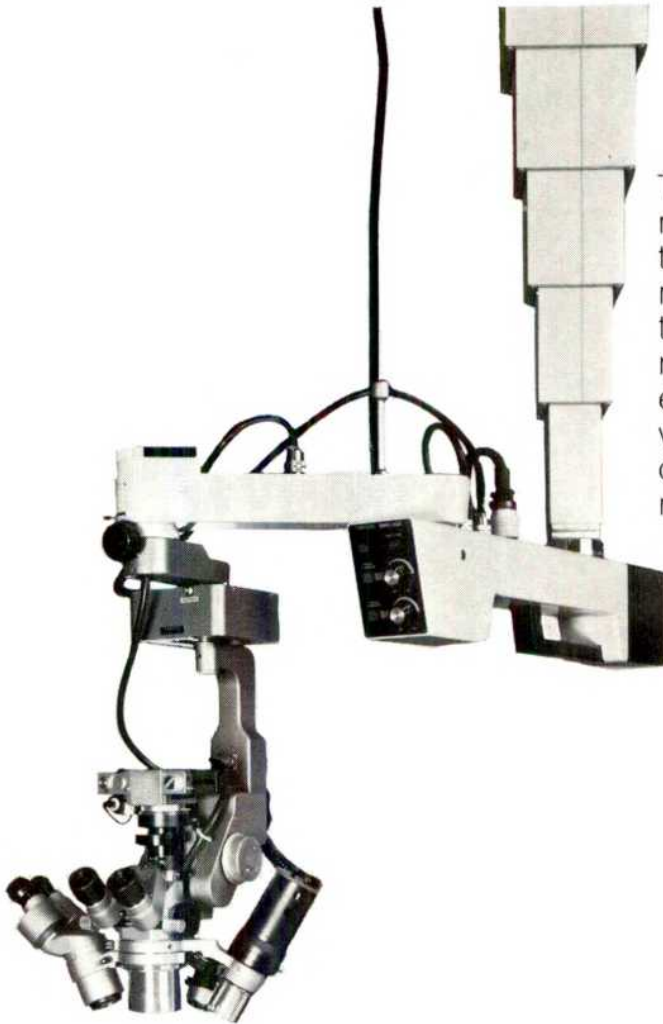
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Editorial: Cataract—is surgery the only solution?

Because cataracts generally occur in the last decade of life this affliction is regarded as a problem peculiar to aging, to be ameliorated or even prevented when aging processes in general are better understood. A few cataracts in younger people are susceptible to biochemical treatment, and these include the 'snow flake' cataract of acute diabetes and the complete opalescent cataract of infantile galactosaemia. However, in senile cataract the major preoccupation of research has been almost entirely biochemical and directed to how the lens fibre proteins age or their membranes become leaky. In biochemical terms this aging process is synonymous with the denaturing and aggregation of the crystallins of the lens.

An in-vivo denaturing protein cannot be restored to normal, so most of the work has concentrated on the nature of the denaturing process in the hope at least of arresting the change at some stage. In this somewhat gloomy situation clinicians have always insisted that for them the only important cataract is one with an opacity in the lens which seriously interferes with vision. The marked yellowing of the lens, even when associated with a good deal of opalescence, is seldom a severe hindrance to vision, because it is mostly confined to the nucleus. Pirie¹ has given an explanation of this yellowing effect, namely, that lens fibre protein macromolecules unfold, the protein becomes more reactive and soluble, but ultimately an insoluble dark brown protein develops. The calcium content has long been known to be increased as the lens ages, and Jedziniak *et al.*² have shown that this will cause an aggregation of lens protein (cystallin); large particles scatter the light strongly and so account for some of the opalescence seen in early cataract.

A paper by Taylor in the present issue (page 303) shows that excessive exposure to ultraviolet light is associated with a marked increase in the incidence of cataract. Borkman and Lerman³ have shown that the tryptophan in lens protein may be broken down, with the production of a free radical. As the nucleus of the lens has a lower concentration of glutathione, the reactive molecule is not neutralised, and a brown nuclear cataract results. An alternative explanation for the difference in colour between the nucleus and cortex is that the nuclear protein of the lens is an embryonic protein formed when the lens had a good oxygen supply from the net of blood vessels surrounding it, whereas protein of

the cortex is laid down in postnatal life under entirely different conditions.

These interesting observations do not help the clinician, who is well aware that a dense brown nucleus is often consistent with excellent vision, provided the centre and particularly the last few layers of the posterior cortex are unaffected. However, once water clefts develop and lamellar separation occurs, vision is seriously reduced. The reason for this increased hydration of the cortex is uncertain, but Fisher⁴ showed that these changes in the cortex are associated with an increased water permeability of the lens capsule, and this may also be reflected in the basement membrane of the lens fibres.

Much of the thinking about the aetiology of cataract has been to answer the question, Why does the lens fibre become opaque? Perhaps it would be better in our search for a medical cure to ask, Can the transparency of an opaque portion of the lens be regained? The clinician often sees a lens which may remain transparent for many years with opacities solely in the posterior cortex associated with an old quiescent uveitis or myopia. The effect on vision is severe, but the thickness of this thin posterior zone remains constant. This seems odd when it is remembered that the lens is laying down new fibres at the front and back of the lens. One would have expected that, if the new fibres were affected, the opacity would thicken, or, if they were unaffected, that a zone of clear fibres would develop adjacent to the posterior capsule. It has to be postulated that either the lens ceases to grow or the fibres recover their transparency as they move away from the affected zone. The work of Fisher and Wakely⁵ has shown that in the rabbit, when the posterior capsule is absent, the exposed lens fibres become oedematous but subsequently appear almost normal when they have been overlaid by another layer of fibres.

However, this still does not answer the question whether transient opacities ever occur in man. Certainly minor traumatic cataract sometimes becomes less after a few months. An interesting family has been reported with an intermittent cataract developing at the posterior pole at the time of presbyopia associated with a congenital defect in the posterior capsule.⁶ This defect was thought to be made leaky by increasing mechanical stress in the lens membranes as presbyopia set in. Confirmation of this idea came from the rapid improve-

ment which occurred when the ciliary muscle was paralysed by atropine. Thus cortical lens opacities may be less permanent than has been previously thought. Both observations suggest lens fibre membrane resists bursting pressure well.⁷

Another paper in this present issue, by Lugaro *et al.* (page 315), gives further credence to this idea, supplemented by another, namely, hormonal influence. The injection of youthful extracts to give vigour to the old has a long history, bedevilled by a good deal of quackery, but it would be unwise to dismiss it out of hand. This photographically documented paper on senile cataract in dogs shows at the very least that advanced cortical cataract is reversible to a marked extent and in a surprisingly short time. Obviously much more work has to be done in isolating the agent responsible for these dramatic changes. However, it would seem that the cortical lens fibre at least can become dehydrated and transparent again, and this gives hope that the

medical treatment of some forms of senile cataract may not be as far off as is commonly supposed.

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The environment and the lens

HUGH R. TAYLOR

From the International Center for Epidemiologic and Preventive Ophthalmology, Wilmer Institute, Johns Hopkins Hospital, Baltimore, USA

SUMMARY The association of various personal, occupational, and environmental factors with cataracts and pseudoexfoliation of the lens (PXF) was examined in a group of Australian Aborigines. Cataracts occurred more commonly in the elderly but were also associated with high levels of ultraviolet radiation and sunlight and were more commonly seen in lower latitudes. PXF was also seen more commonly in the elderly, especially among males. PXF occurred particularly commonly in stockmen and was related to latitude and global radiation. It was positively associated with the occurrence of cataract and with climatic droplet keratopathy. It is suggested that senile cataracts are related to the amount of ultraviolet radiation and PXF to global radiation.

The eyes of Australian Aborigines in outback Australia are exposed during waking hours to an atmosphere of low humidity and often of high temperature, and in particular to intense solar irradiation. Both senile cataracts and pseudoexfoliation of the lens (PXF) have been reported as occurring commonly in Australian Aborigines.^{1,2} While it has been suggested that senile cataracts, in particular nuclear sclerosis, may be related to environmental factors, including solar radiation,³⁻⁶ no epidemiological studies have demonstrated a clear association with ultraviolet radiation. PXF has a marked regional variation in its distribution,^{1,6-9} but the possibility of an environmental cause had not been considered.

The following study investigated the role of a number of personal and environmental factors in the causation of these 2 conditions. It was conducted as a separate study in conjunction with the routine field work performed by the National Trachoma and Eye Health Programme (NTEHP).

Materials and methods

The methods used to select people for inclusion in this study and the examination procedure have been described in detail.^{2,10,11} Briefly, 350 Aborigines over the age of 30 were studied. They were selected from either a sampling of 2 aboriginal communities or were included in a case-control study of blindness. A detailed personal history was obtained and

slit-lamp examination performed. Intraocular pressure was measured with either a Goldmann or Perkins applanation tonometer.

The presence of lens opacities was determined by slit-lamp examination. The severity of lens opacities was graded according to the degree of reduction of visual acuity attributable to those opacities: grade 1, visual acuity correctable to 6/6; grade 2, visual acuity correctable to better than 6/60 but less than 6/6; grade 3, visual acuity correctable to 6/60 or less. The data presented in this study are for grade 2 and grade 3 opacities. In bilateral cases the patient was classified according to the poorer eye.

Environmental data for the place of residence for each person were obtained from published records.¹²⁻¹⁵ The test of statistical significance used throughout was the chi-square test. For simplicity only the P values are presented in the text. It must be remembered that the associations of many variables were tested.

Results

SENILE CATARACTS

In the 350 individuals studied 116 people (64 males and 52 females) were found to have lens opacities other than traumatic cataract. One hundred and three of these cataracts were either nuclear or mature cataracts, and a further 7 were hypermature. No significant sex correlation was found, but this may have been masked by the matching used in the case-control study of blindness.

The finding of cataracts was strongly age related (Table 1, Fig. 1). No correlation was found between

Correspondence to Dr H. R. Taylor, Wilmer Institute, Johns Hopkins Hospital, Baltimore, Maryland 21205, USA.

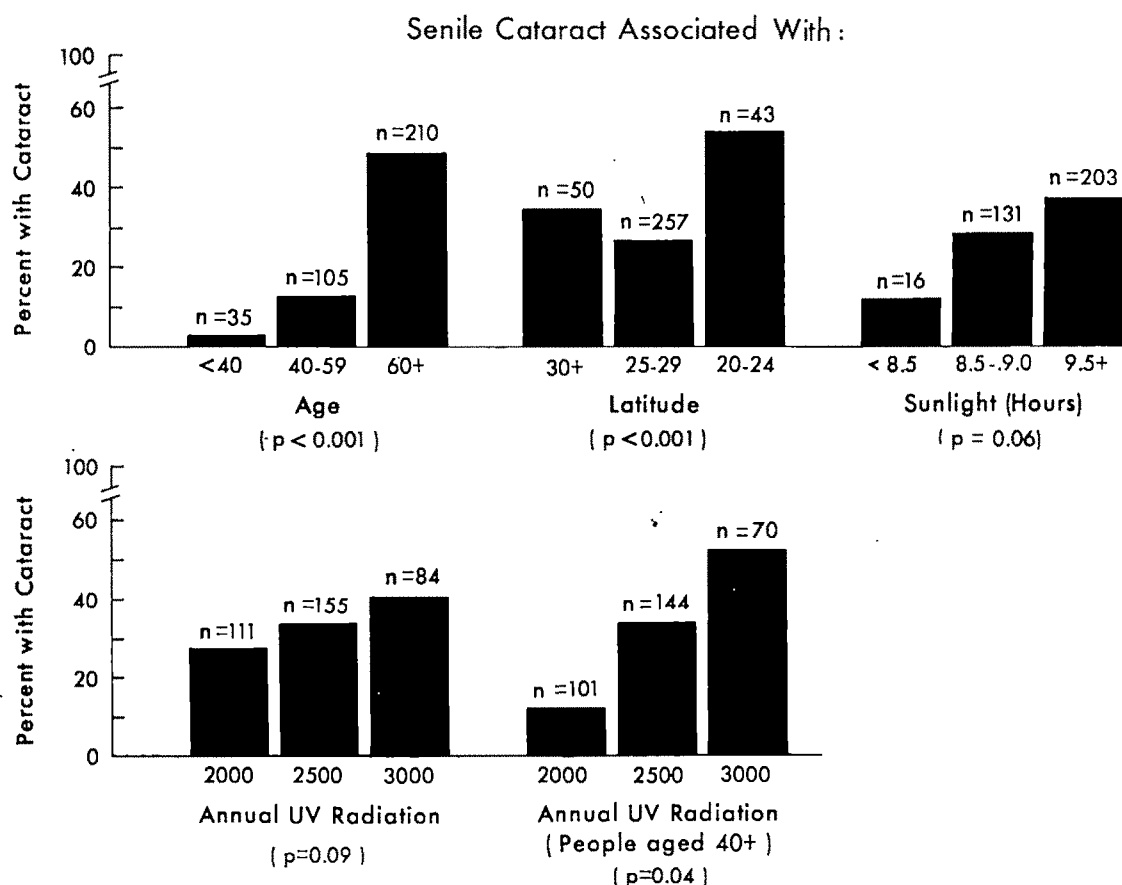


Fig. 1 Histograms showing the prevalence of senile cataracts in 350 Aborigines by age (years), latitude (degree), annual mean daily hours of sunlight, annual mean ultraviolet-B radiation (mean erythemal doses); the latter is also shown for 315 Aborigines over the age of 40.

Table 1 Distribution of cataract by age in 350 Aborigines*

Age (years)	Cataract		
	Present	Absent	Total
Below 40	1	34	35
40-59	13	92	105
Above 60	102	108	210
Total	116	234	350

* χ^2 , 2DF = 57.5; $P < 0.001$.

occupation, a history of alcohol intake, or ocular trauma, either in the group as a whole or for each age and sex group.

For both those aged 40-59 and those over the age of 60 years no relation was found between the severity of trachoma signs and cataracts (Table 2).

Table 2 Distribution of cataract by severity of trachoma and trichiasis in 315 Aborigines over the age of 40

	Age 40-59 years			Age 60+ years		
	Cataract			Cataract		
	Present	Absent	Total	Present	Absent	Total
Trachoma scarring						
Index ^{1*}						
Nil	0	0	0	1	2	3
Negligible	3	14	17	1	10	11
Mild	5	48	53	37	36	73
Severe	5	30	35	63	60	123
Trichiasis	2	2	4	12	18	30
Total	13	92	105	102	108	210

A strong association was found between cataracts and latitude, with cataracts being more common at lower latitudes (Table 3, Fig. 1). A trend existed for cataracts to be associated with a greater number of hours of sunlight per day (Table 3, Fig. 1), those with less than 8 hours of sunlight having fewer cataracts than those with 8.5 hours or more. A trend was also found for cataracts to occur more often in areas with higher annual mean ultraviolet-B radiation levels (Table 3, Fig. 1). This association was statistically significant when those over the age of 40 were examined separately (Table 4, Fig. 1). Only 1 person under the age of 40 had a cataract.

No relation was found to exist between the presence of cataract and the following environmental factors: maximum temperature, evaporation rate, relative humidity, and total global radiation for January or the year, or annual rainfall. There was no age correlation with these factors.

In all, 14 cases of traumatic cataract were seen. These have not been included in the preceding analysis. All these traumatic cataracts were unilateral. Ten occurred in males and 4 in females. Nine cases followed blunt trauma, 2 followed penetrating trauma, and in 3 the nature of the trauma was unknown. Four occurred in childhood, 3 in adolescence, 6 in young adults, and only 1 over the age of 40. The ages of the patients seen ranged from 22 to about 70 years. The causes of blunt trauma included: fights, stones, and being

Table 3 *Distribution of cataract in 350 Aborigines according to latitude, mean daily hours of sunlight, and annual mean ultraviolet radiation (mean erythral doses)**

	Cataract			Relative risk
	Present	Absent	Total	
<i>Latitude</i>				
20°-24°	23	20	43	2.2
25°-29°	76	181	257	0.8
Above 30°	17	33	50	1.0
<i>Sunlight hours</i>				
8 or less	2	14	16	1.0
8.5-9	38	93	131	2.9
9.5 or more	76	127	203	4.2
<i>Ultraviolet dosage</i>				
2000	30	81	111	1.0
2500	52	103	155	1.3
3000	34	50	84	1.8
Total	116	234	350	

*Latitude: χ^2 , 2DF=9.53; $P=0.009$. Sunlight: χ^2 , 2DF=5.78; $P=0.06$. Ultraviolet: χ^2 , 2DF=3.92; $P=0.14$. χ^2 , 1DF (<2500 vs. 3000)=2.74; $P=0.09$.

Table 4 *Distribution of cataract in 315 Aborigines over the age of 40 according to annual mean ultraviolet radiation (mean erythral dose)**

Ultraviolet dosage	Cataract			Relative risk
	Present	Absent	Total	
2000	30	71	101	1.0
2500	51	93	144	1.3
3000	34	36	70	2.3
Total	115	200	315	

* χ^2 , 2DF=6.49; $P=0.04$. χ^2 , 1DF (<2500 vs. 3000)=5.65; $P=0.02$.

hit by a whip. The types of penetrating injury included injury from a stone, from chopping wood, and from tree branches.

PSEUDOEXFOLIATION OF THE LENS

Thirty-four cases of pseudoexfoliation of the lens capsule (PXF) were seen. Twenty-six cases occurred in males and 8 in females, and the sex correlation was statistically significant ($P<0.001$, Fig. 2). Twenty-nine of the patients were over the age of 60 years, and this increase in prevalence with age was statistically significant (Table 5, Fig. 2). There was no tribal clustering of PXF.

In only 1 case was the intraocular pressure elevated. This occurred in a 66-year-old male who has unilateral PXF with a hypermature cataract and with an open angle. The presence of the cataract prevented examination of his disc. Because of examination conditions detailed visual-field assessment was not possible, but his fields appeared full on confrontation testing. The unilateral elevation of intraocular pressure may have been related to the hypermature cataract.

Occupation was related to the finding of PXF; there was a much higher prevalence of PXF among stockmen than in those who had other occupations or who had not worked ($P=0.006$; Table 6, Fig. 2).

PXF was seen more often in the lower latitudes; those living in the more northern areas had a significantly higher prevalence of PXF than those living further south ($P=0.03$; Table 7, Fig. 2). The annual total global radiation level was also associated with PXF (Table 8); persons receiving more than 600 mW/h/cm² had more cases of PXF than those living in areas receiving less irradiation ($P=0.07$ for the group as a whole; $P=0.06$ for males over the age of 60; Fig. 2). Males over the age of 60 were examined separately because PXF occurred most frequently in this group.

No consistent association existed between the environmental factors of maximum temperature,

Table 5 *Distribution of pseudoexfoliation by age**
in 350 Aborigines

Age (years)	Pseudoexfoliation		
	Present	Absent	Total
0-39	0	35	35
40-59	5	100	105
60 and over	29	181	210
Total	34	316	350

* χ^2 , 1DF (less than 59 vs. 60 and over) = 10.04; $P=0.001$.Table 6 *Distribution of pseudoexfoliation by occupation in 350 Aborigines*

Occupation	Pseudoexfoliation		
	Present	Absent	Total
Not employed	20	195	215
Stockman	9	33	42
Station hand	3	35	38
Other	2	53	55
Total	34	316	350

* χ^2 , 1DF (stockmen vs. others) = 7.47; $P=0.006$.

evaporation rate, relative humidity, annual rainfall, hours of sunlight, or ultraviolet radiation. This was true for analyses using the annual means, midsummer (January) and midwinter (July) values of these variables.

Pseudoexfoliation and climatic droplet keratopathy were significantly linked when the group as a whole was examined ($P=0.002$). Because both conditions were found frequently in stockmen, this association may have been factitious. However, when stockmen were analysed for the occurrence of pseudoexfoliation and climatic droplet kerato-

Table 7 *Relation between pseudoexfoliation and latitude (degrees) in 350 Aborigines**

Latitude	Pseudoexfoliation		
	Present	Absent	Total
20-24	8	35	43
25-29	25	232	257
30-35	1	49	50
Total	34	316	350

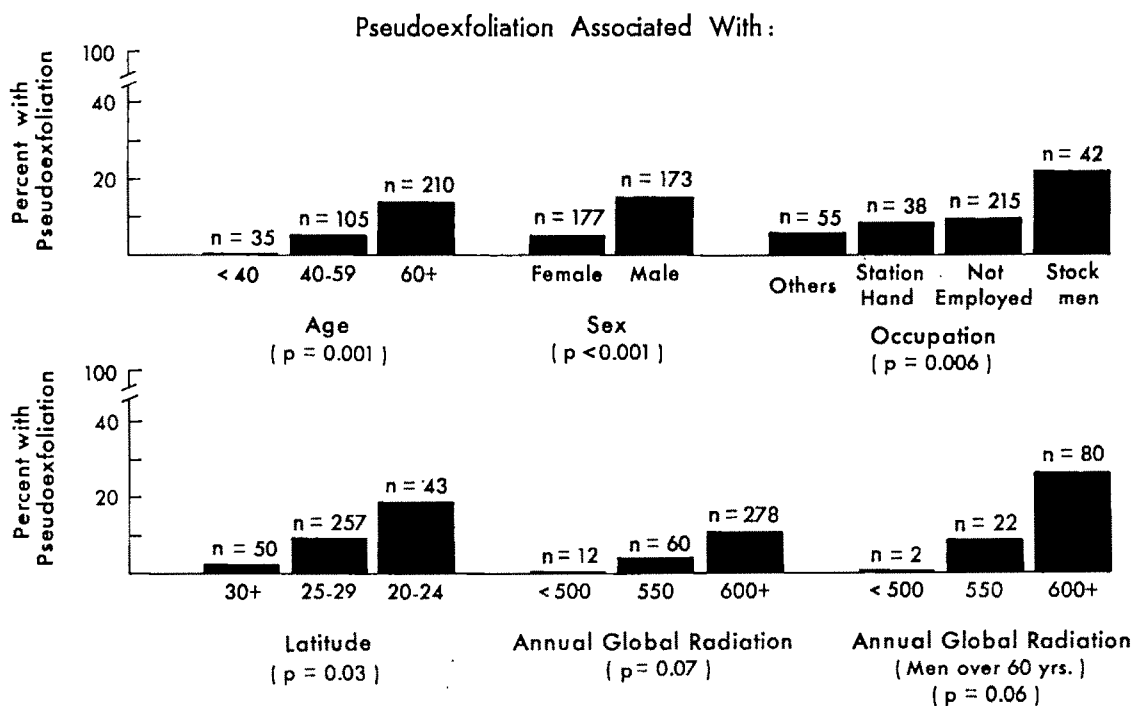
* χ^2 , 2DF = 7.27; $P=0.03$.

Fig. 2 Histograms showing the prevalence of pseudoexfoliation in 350 Aborigines by age (years), sex, occupation, latitude (degree), annual mean daily total global radiation ($mW/h/cm^2$); the latter is also shown for 104 males over the age of 60.

Table 8 *Relation between pseudoexfoliation and annual total global radiation (mW/h/cm²) for 350 Aborigines and for 104 males over the age of 60**

Global radiation	All ages			Males 60+ years		
	Pseudoexfoliation			Pseudoexfoliation		
	Present	Absent	Total	Present	Absent	Total
500 or less	0	12	12	0	2	2
550	3	57	60	2	20	22
600 or more	31	247	278	21	59	80
Total	34	316	350	23	81	104

* χ^2 , 1DF (550 or less vs. 600 or more) = 3.18; $P=0.07$ (all ages); = 3.44, $P=0.06$ (men over 60).

Table 9 *Relation between pseudoexfoliation and climatic droplet keratopathy in 42 stockmen**

Climatic droplet keratopathy	Pseudoexfoliation		
	Present	Absent	Total
Present	7	11	18
Absent	2	22	24
Total	9	33	42

* χ^2 , 1DF = 5.70; $P=0.02$.

Table 10 *Relation between pseudoexfoliation and cataract in 210 Aborigines over the age of 60**

Cataract	Pseudoexfoliation		
	Present	Absent	Total
Present	20	82	102
Absent	9	99	108
Total	29	181	210

* χ^2 , 1DF = 5.60; $P=0.02$.

pathy (Table 9), this significant correlation still remained ($P=0.02$).

Pseudoexfoliation was also significantly associated with the presence of cataracts. Because both these conditions were more common in the elderly, those over the age of 60 were examined separately (Table 10). Pseudoexfoliation and cataracts were still significantly associated in those over the age of 60 ($P=0.02$).

Discussion

CATARACT

Although many specific disorders are known to be associated with cataract formation, these account for only a small proportion of the total number of cataracts. The majority of cataracts fall into the

so-called 'senile' group, for which no cause is known.

The global distribution of cataracts is difficult to determine.¹⁸ This is in part due to the variation in definition of cataracts, and is also due to the samples that have been studied. Kahn *et al.*¹⁷ defined cataract as lens opacities, excluding certain small embryonal and dot opacities, in eyes with a best visual acuity of 20/30 or less. Kornzweig *et al.*¹⁸ classified cataracts on a different set of visual acuity gradings and excluded eyes with associated glaucoma or macular diseases. Milne and Williamson¹⁹ defined cataract as any opacity in the lens of either eye. Brennan and Knox²⁰ used the criterion of lens opacities that caused people to present for cataract surgery, whereas Chatterjee²¹ based his diagnosis on the 'simultaneous diminution of the fundal glow with diminished visual acuity'.

The populations studied have also varied greatly—from large population surveys²¹ to small, carefully selected random samples,^{17,18} the occupants of old people's homes,¹⁸ outpatients attending an eye clinic,²² or inpatient surgical cases.²⁰

The present analysis examined data collected for two previous studies.^{8,10} Because of the selection methods used, no inference can be drawn about the overall prevalence of cataracts or PXF in the population studied, although investigation into the role that personal and environmental factors play in causation of these 2 conditions is valid.

The obvious relation between the prevalence of cataract and ageing was clearly shown in this study. Cataracts were found to occur as commonly in males as in females. In previous studies no consistent sex difference has been found. Reports finding both more males with cataracts¹⁷ and more females¹⁹ have been published.

The relation between cataract and latitude, hours of sunlight, and ultraviolet radiation (UV-B) is of greater interest. In general, ultraviolet radiation increases directly with hours of sunlight and indirectly with latitude. Therefore latitude and sunlight act as indirect markers of ultraviolet radiation. The relationship between these 3 parameters and cataract shows a clear and consistent dose-response with a progressive increase in relative risk. This indicates the validity of the association, though all did not reach statistical significance by chi-square testing. Although both ultraviolet radiation and global radiation tend to be positively related to latitude and sunlight, they have different distributions in the area studied. As cataract was not related to global radiation, the specificity of the association with ultraviolet radiation is strengthened.

The data on the distribution of ultraviolet

radiation in Australia have only recently become available.¹⁵ As yet comparable data do not exist for any other continent.

Several previous epidemiological studies have indicated that some forms of radiant energy, particularly sunlight, may be associated with cataract formation.⁴⁻²³ Similar evidence comes from studies of the prevalence of cataracts in different areas. Cataracts are particularly common in tropical areas.³⁻¹⁶⁻²¹⁻²²⁻²⁴⁻²⁵ In northern temperate areas it appears that cataracts are found in about 20% of those aged between 65 and 75 years¹⁷⁻¹⁹ and that they are seen even more uncommonly in more northern subarctic areas.²⁶⁻²⁷

The study of Chatterjee²¹ is particularly interesting. He found a higher prevalence of cataracts in the Punjabi plains of India than in the higher altitudes of the Himalayas. Many factors may play a role in this difference, including genetic variation and environmental effects such as the mineral content of water, yoghurt consumption, and socio-economic variables. (Richter and Duke²⁸ produced cataracts in rats fed on commercially manufactured yoghurt which had a high galactose content.) As altitude increases, there is usually an increase in the radiant energy, especially ultraviolet radiation, and Chatterjee's figures have been used to suggest that ultraviolet radiation is not related to the development of cataracts. However, Chatterjee himself mentions that the middle Himalayan area often has a heavy cloud cover. Although a light cloud cover does not block a significant amount of ultraviolet radiation, a heavy cloud cover may.²⁹ The data are not available on either the hours of sunlight or the ultraviolet radiation levels in the areas studied by Chatterjee, and the significance of his findings as they relate to the effect of radiation cannot yet be determined. Interestingly, Vines³⁰ found a higher prevalence of cataracts in the highlands of New Guinea than he found in the lower plains.

Pirie⁵ has demonstrated that human lens proteins turn brown in direct sunlight, and that this is the result of photo-oxidation. She showed that this photo-oxidation was caused by light of wavelengths between 300-320 nm (i.e., ultraviolet-B radiation). There exists in the lens a reducing system to reverse this photo-oxidation of the lens proteins. The reducing substances of most importance are thought to be glutathione and ascorbic acid.³¹ It may be that this reducing system, or at least its efficiency, decreases with age. If the photo-oxidised proteins are not reduced, they form covalent bonds, especially disulphide bonds, with other lens proteins. This cross-linkage formation between lens proteins leads to the formation of insoluble protein com-

plexes.³¹⁻³² It has also been possible to produce lens changes with ultraviolet light in short-term in-vitro experiments.³³⁻³⁴

Although there is biochemical evidence suggesting that senile cataracts may be caused by the cumulative ultraviolet-induced photo-oxidation and cross-linkage of lens proteins, no previous study was found that had examined the association between environmental ultraviolet levels and cataract. Thus the finding of an association between cataract and ultraviolet radiation in this study provides this epidemiological evidence.

The effect of nutrition on cataractogenesis is uncertain. Pirie³⁵ suggested that poor nutrition, especially a riboflavin deficiency, may be important in the formation of cataracts, but others have believed that nutrition is less important in this regard.²¹⁻²⁵ The diet and nutritional status of the Aborigines examined in this study were essentially uniform. It is noteworthy that riboflavin deficiency is not uncommon in alcoholics,³⁶ and it is the author's experience that young people with senile cataracts are often alcoholic. This observation has also been made by Hollows (personal communication). In this study, however, no association was found between the presence of cataracts and alcohol consumption.

It has been suggested by some that diabetics have a higher incidence of senile cataracts than non-diabetics,³⁵⁻³⁷⁻³⁸ but others have disagreed with this finding,³⁹ or suggested that diabetics are only more likely to have cataract surgery.⁴⁰⁻⁴¹ Australian Aborigines have a high prevalence of diabetes, but this has not been associated with an increased prevalence of cataracts.⁴²⁻⁴³

Several interesting correlations with the presence of senile cataract were found in the Framingham Eye Study.¹⁷ As a group, people with cataract were found to have had a lesser amount of education, to have a higher blood sugar, higher blood pressure, a smaller vital capacity, decreased mean grip strength, and to be of shorter height as compared to those without cataracts. It is possible that the reduction in height, vital capacity, and grip strength are all related, inasmuch as they are all known effects of ageing. The association of an elevated casual blood sugar, hypertension, and elevated phospholipid levels may all be secondary associations with diabetes, ageing, or even alcoholism. A lower level of education may have caused these people to seek a manual or outside occupation and thus result in their being exposed to higher levels of sunshine and thus an increased risk of developing cataract. The exact relevance of these findings is not yet clearly understood, though they open up an interesting field for further study.

PSEUDOEXFOLIATION

The prevalence of pseudoexfoliation of the lens capsule (PXF) was found to increase with increasing age. This association between PXF and ageing has been previously described.⁶ The common finding of cataract with PXF and the infrequent finding of glaucoma with this condition in the Australian Aborigines have been previously reported.¹ The infrequency with which glaucoma is found is even more striking, as it has been suggested that glaucoma is common in eyes with trachoma.⁴⁴ This study has confirmed the earlier findings related to PXF in Aborigines and has quantified the frequent association with cataract.

The association of PXF with various environmental factors—in particular those factors relating to radiation effects such as latitude and yearly global radiation levels—was unexpected. After examination of previous reports,⁹ the possibility of an environmental factor such as radiation does not seem so unusual, because the highest prevalence of PXF reported by Forsius was found in the Lapps, who live around the Arctic Circle. Lower prevalences were found in more southerly areas of northern Europe, although Forsius and Luukka⁴⁵ felt that PXF was not related to latitude. Similarly, the relatively high prevalence of PXF in the African Bantus⁸ and the lower prevalence of PXF in the American Negroes⁷ could possibly be explained by environmental factors, because these groups share a common genetic background. The association observed between PXF and senile cataract and climatic droplet keratopathy would also suggest that PXF may be radiation induced.

The PXF material is known to be banded fibrillary protein^{46–48} and that it is histochemically, immunologically, and ultrastructurally similar to amyloid^{48,49} and is not derived from collagen.⁵⁰ It has been suggested that the material is an altered basement-membrane protein,^{48,51} possibly elaborated by the pre-equatorial lens epithelium.

Seland⁵² has shown that the abnormal material can definitely be elaborated by the lens epithelium. Others have pointed out that the material is also seen in the iris, ciliary body, and subconjunctiva, and that the formed material could not migrate there because of its size.^{51,53,54} Eagle and co-authors⁴⁸ have also demonstrated the likelihood that the PXF material, or precursor, is elaborated by iris and ciliary epithelium. It has been postulated that a circulating substance in the aqueous is somehow stimulated to form the PXF material.^{54,55} Sugar and others⁵¹ considered that ageing alone was the stimulus, while Dark and co-workers⁴⁶ have postulated that some as yet unidentified lysozymal enzyme may be responsible. It may well be that the causative stimulus is provided by radiation.

It is postulated, therefore, that basement-membrane precursors are elaborated by the epithelial cells lining the anterior segment of the eye. These diffuse into the aqueous and are denaturated by irradiation. These denatured proteins then polymerise and are deposited on the intraocular surfaces particularly the lens capsule. Some denatured proteins also pass into the extracellular spaces of the adjacent structures (the iris, ciliary body, and subconjunctiva) and form agglomerations there. An alternative pathway may be that these epithelial cells produce abnormal basement-membrane precursors as a result of radiation-induced changes. These precursors may then polymerise spontaneously.

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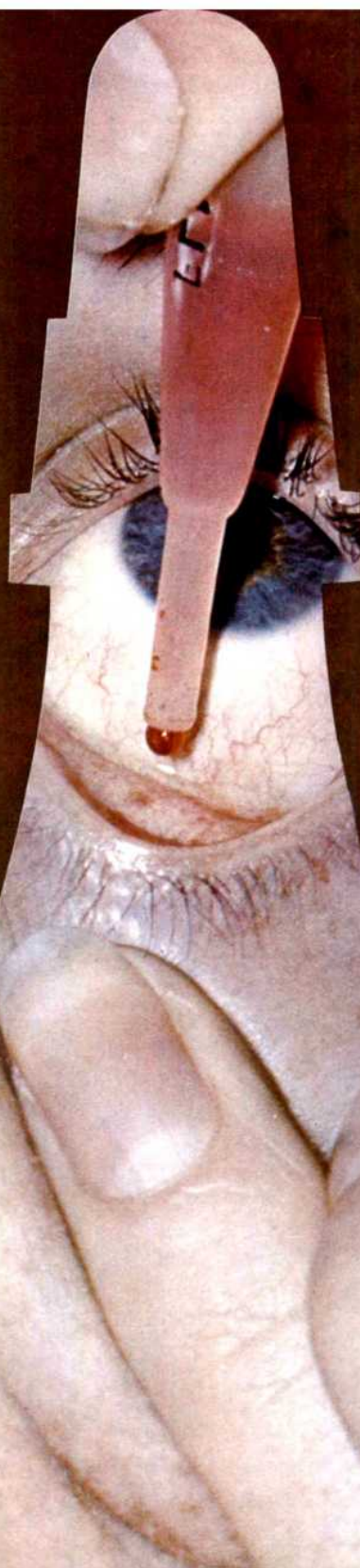
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P175-UK-Feb 80

PARKE-DAVIS

A note on a possible relation between refraction and a disposition for senile nuclear cataract

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SUMMARY A study was made of records of patients who have had at least 1 senile cataract removed and for whom refraction records were available. The risk of a cataract occurring was determined as a function of precataractous refraction. Emmetropia was found to provide a sharp borderline between the low risk (about 1:1000) of hypermetropes and an increasing risk (about 1:100) for moderate myopes for patients in their early 60s.

Fisher's interesting study on phakochronometry¹ has made it likely that the formation of some types of senile cataract have a physical component attributable to ciliary stress. This is true particularly of the coronal type. Fisher² also distinguished two maturation periods, for senile nuclear and coronal cataracts respectively, the former having the shorter period.

There are, however, some long-term mechanical considerations which may modify a disposition due to a variety of other causes. One obviously faces the question whether there is a relation between the presenile refraction of an eye and the risk of cataract in that eye. A priori we know that hypermetropic lenses tend to be latently accommodated, that is, subject to less zonular stress than is true of myopic ones. Yet apparently no study has been made to determine what relation, if any, exists between the 2 variables.

This is partly owing to the sparseness of relevant clinical data and appropriate controls. The present note is intended not to provide a solution to the problem of a possible relation between refraction and (subsequent) senile cataract but rather to draw attention to it in the hope that the compilation of relevant records may provide a valid data base. Meanwhile records for over 200 eyes were analysed in an attempt to show that such an endeavour might be fruitful.

The study necessitated a knowledge of the refraction frequency distribution of the noncataractous population for a comparable age group. Of the few sets available Brown and Kronfeld's data³ were selected for this purpose (Fig. 1A). The known

statistical variations of refraction with age⁴ does not significantly affect the issue under discussion.

Materials and methods

The test data were obtained from the records of Moorfields Eye Hospital. Only those records were used where a cataract had been extracted at least on one side. The last refraction measurement before the operation was recorded, with its date and in addition, wherever possible, very much earlier or precataractous refractions. Only senile cataracts were considered: wherever there was a complication, such as diabetes, etc., the data were discarded. The protocol having been laid down, the records were examined by a lay assistant who was unaware of the framework of the study so that all bias could be minimised.

Results

The frequency distribution of the estimated minimum maturation periods is shown in Fig. 2. The median occurs at 3 years, and, if we bear in mind the expected skewness of the distribution, this agrees well with Fisher's estimate of 4 years for nuclear cataracts.

Fig. 1B shows the raw distribution for preoperative refractions. It is clear that there is a heavy bias on the myopic side of zero. However, as the development of nuclear cataract is accompanied by an increase in negativity,⁵ Fig. 1B has to be corrected if the precataractous refractions are to be assessed.

The analysis of the records yielded an estimate between the preoperative refraction and the rate in dioptries per annum at which this was reached

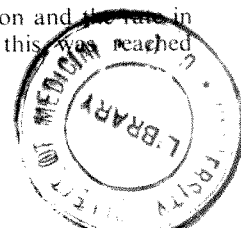
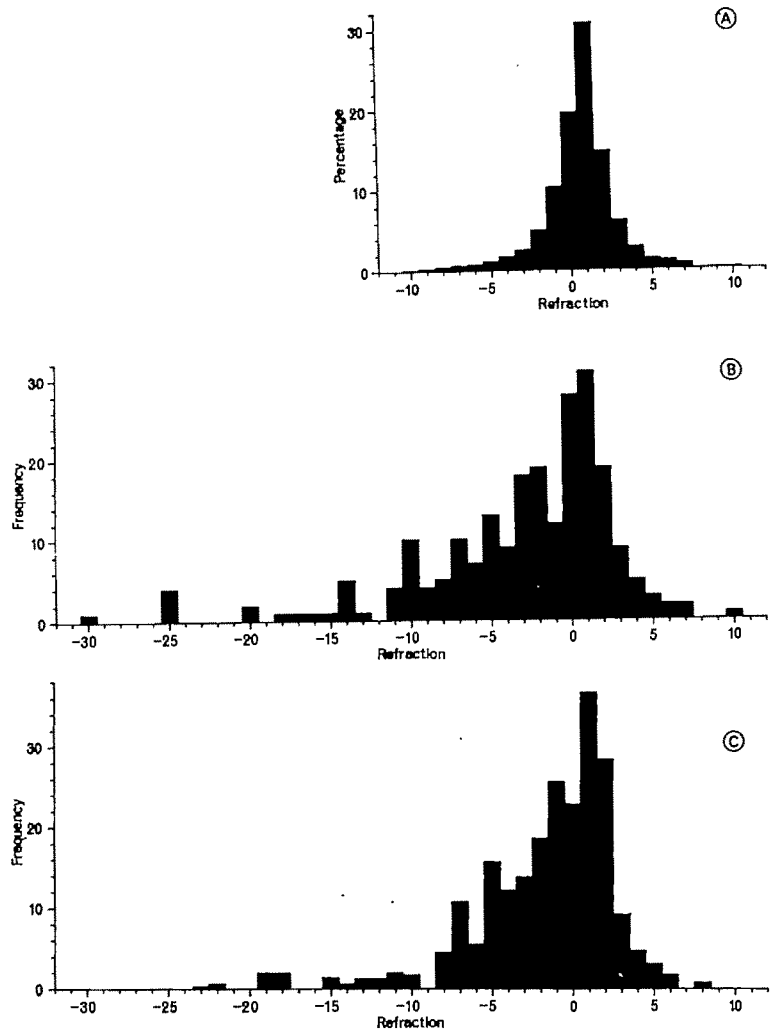


Fig. 1 Population distributions of refractive states. A. Brown and Kronfeld's data³ for a normal presbyopic population. B. Data for final preoperative refractions in cases of senile cataracts. C. The same after a correction for myopisation has been applied on the assumption that the maturation period is 3 years (cf. Fig. 2) and that the annual change in refraction as a function of refraction is given by Fig. 3.



(Fig. 3). This step was needed to arrive at an estimate of the presumptive precataractous refraction (see below). The slope of the regression differed significantly from zero ($P < 0.001$) and shows that the more myopic the eye to begin with the greater the rate of development of nuclear myopia. This result is based on the difference between preoperative and precataractous refraction measurements divided by the time interval elapsing between them.

The analytical procedure was as follows. Let the fraction of the total population of a given age group having a refraction D_1 be $p(D_1)$ so that

$$\sum_n^m p(D_n) = 100.$$

The corresponding fraction for a coeval preoperative group is $p'(D_1)$ with an analogous sum. Fig. 2

shows that the median for the presumptive maturation period is 3 years. With a statistical estimate for the annual myopisation $\Delta(D)$ obtained from the data shown in Fig. 3 the mean estimated minimum

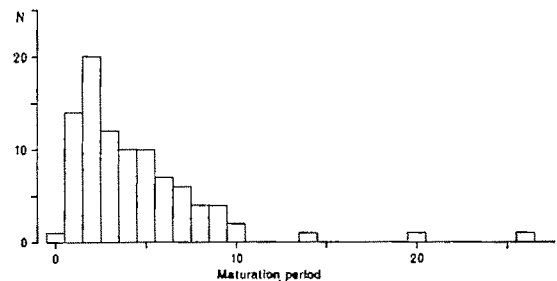


Fig. 2 Distribution of maturation periods for nuclear cataracts.

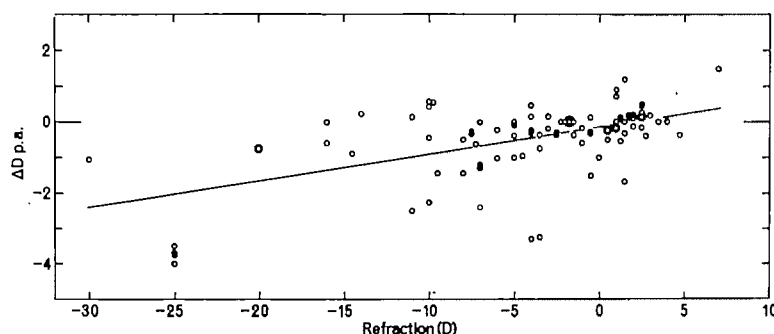


Fig. 3 Rate of change of refraction as a function of the refractive state after a cataract has been diagnosed.

change in refraction during the maturation period is $3\Delta(D)$, where D is the preoperative refraction. The value $3\Delta(D)$ is therefore subtracted from D . This gives an estimated frequency distribution for the precataractous group with percentage values of $p^*(D_1)$.

The simplification of assuming an average maturation period of 3 years is safe, as the statistical significance of the following considerations is unimpaired even if this period is hypothetically doubled ($P < 0.001$). The corrected frequency distribution is shown in Fig. 1C. The precataractous area under the resultant histogram is proportional to the total population, that is, the population that is going to suffer from cataract. Normalisation is achieved by scaling all the P values by a factor so chosen as to make the area equal to that for the normal noncataractous population. It is noted that the latter may contain potential cataract patients, as it refers to a relatively young population. So far from invalidating the argument, this actually strengthens it: if, as the data suggest, myopia increases the hazard of cataract, the 'immune' population must be hypermetropic in relation to the normal distribution which has not presented.

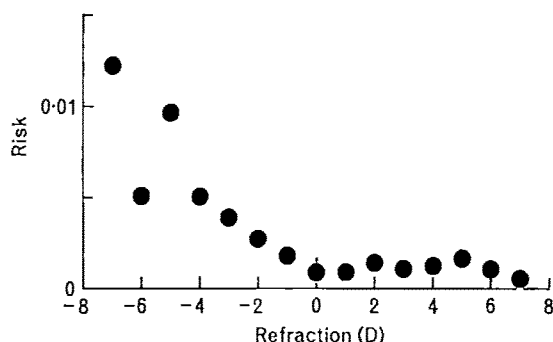


Fig. 4 The risk of a lens being extracted owing to a cataract as a function of ocular refraction. It represents the ratio of the ordinates in Figs. 1C and 1B, and is scaled as explained in the text.

$p^*(D_1) \div p(D_1)$, that is, the ratio of the fraction of precataractous persons with a refraction D_1 and the fraction of 'normal' persons having the same refraction provides a measure of the risk of cataract as a function of refraction. The actual risk is obtained by multiplying this value by the incidence of senile cataract at the corresponding age obtained as set out below.

Discussion

It would seem that this is the first time a link between axial (?) and refraction myopia has been observed. This is not to suggest that there is a direct causal connection between the two, but a sequence of possibilities based on the introductory considerations cannot be ruled out.

It can be shown on the basis of 3 detailed studies of the incidence of cataract⁶⁻⁸ that, to a first approximation, the risk R of a cataract is 1:2500 at the age A of 50 years, and 1:10 at $A=100$ years. In general,

$$\log R + 5.8 = 0.048A$$

At the average age of the cataractous population ($\bar{A}=64.23$ years, $\sigma=9.55$ years), the risk is therefore 1:600. Multiplication of the aforementioned ratios by this overall risk yields the values shown in Fig. 4.

This tells us with surprising clarity that the merest trace of myopia increases the risk: at relatively moderately small defects the risk rises 10-fold over the minimum (normal) value. Qualitatively the result is consistent with the predictions based on laboratory tests⁹ and calls for an examination of the influence of other controllable parameters.

If the causal nexus is valid, then it may well become necessary to over-correct myopes, say, in their late 20s or early 30s so as to maintain their lenses in a slightly accommodated state. Attention would then also have to be given to the oculomotor balance.

My thanks are due to the surgeons of Moorfields Eye Hospital for allowing records of their patients to be used.

I also thank Miss G. M. Villermet for her help, Mr H. Donovan for computational assistance, and the H. C. Binstead Memorial Fund for financial support.

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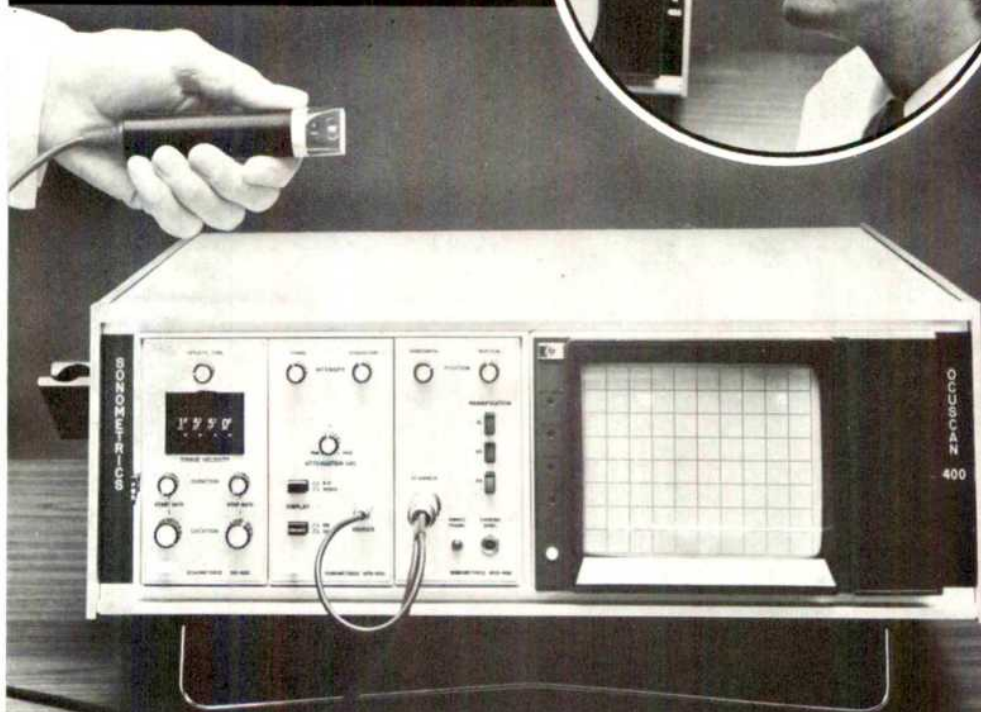
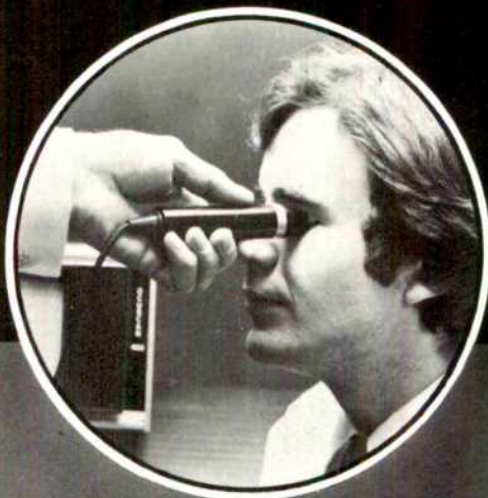
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Effect of a nonsteroidal gametic factor on senile cataract in the dog

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SUMMARY We have studied the clarifying activity of a purified peptide fraction of gametic origin in senile cataract of the dog. The active substance, administered intramuscularly, had significant and durable clarifying effects on the cortical area of the lens.

We have reported^{1,2} that the male gamete contains one (or more) active substance(s) which counteract(s) temporally and partially some dysfunctions normally occurring in the later part of mammalian life, namely, the so-called senescence phenomena. Since the appearance of senescence varies greatly from individual to individual and is highly time-dependent, we decided to analyse one of the more frequent structurally irreversible changes, spontaneous senile cataract, a syndrome that may be evaluated semiquantitatively.

When dogs suffering from senile cataract are injected intramuscularly either with whole homologous semen¹ or with steroid-, nucleic acid-, and protein-free aqueous extracts of homologous or heterologous spermatozoa,³ their condition shows a marked remission. We therefore decided to reinvestigate this problem from the point of view of new data we have obtained during recent years.

Material and methods

The spermatozoa, obtained after centrifugation at 700 *g* of bull's semen, were washed twice with saline. After homogenization with corindone and centrifugation at 5000 *g*, the pooled supernatants (step I) were ultrafiltered through a membrane with a porosity of less than 5 nm (molecular weight cut off = 10 000 daltons). All steps were carried out at 2°C.

The ultrafiltrate (step II) was chromatographed on a DEAE-cellulose column at pH 5, with 0.005 M ammonium acetate-acetic acid buffer, and a linear

gradient up to 0.5 M ammonium acetate.⁴ The eluate was divided into 5 fractions; the first eluted fraction (step III), containing the bulk of the activity, was enriched in peptides and free amino acids. The oligonucleotides were eluted with the application of the gradient.

Aliquots of lyophilised fraction from step III, solubilised in 0.005 M ammonium acetate-acetic acid buffer at pH 4.5, were chromatographed according to the method of Gianfranceschi *et al.*⁵ on spermatozoan-DNA cellulose column prepared as described in Litman.⁶ The active fraction (step IV), eluted in 0.005 M ammonium acetate-acetic acid buffer at pH 4.5, was rechromatographed, after lyophilisation, on Dowex 50 W×2 column, yielding at pH 4.5 a highly purified fraction (step V). (The same highly purified fraction has been obtained from calf thymus (Gianfranceschi G. L., personal communication), which is a poorer but easily extractable source.)

All the fractions obtained at various stages of purification were assayed intramuscularly (2 injections every 12 hours) in senile dogs, 10 or more years old, suffering from spontaneous bilateral corticonuclear opacity of the crystalline lens. 24 hours before and 24 hours and seven days afterwards the eyes were observed with a slit-lamp and with ophthalmoscope under standard conditions at maximum mydriasis in all cases.

We have expressed the results thus obtained semiquantitatively, using an arbitrary scale as follows: (-), nondemonstrable effects; (+), slight and limited clarification of cortical regions in the crystalline lens (approximately 15% decrease of total opaque area); (++) , marked clarification (approximately 30% decrease); (+++) , almost

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Table 1

Fraction injected	No. of animals	Dose (as spermatozoa equivalent/kg bodyweight)*	Assessment of improvement 24 hours later**
Step II	8	2×10^8	$-(-, -, +\pm, +\pm, -, -, +, +\pm, +\pm, +\pm, +\pm)$
Step III	8	2.5×10^8	$+ \pm \pm (+\pm\pm, +\pm, +\pm, +\pm, +\pm, +\pm, +\pm, +\pm)$
Step III, after trypsin digestion	4	2.5×10^8	$-(-, \pm, -, -)$
Step III, after papain digestion	3	2.5×10^8	$-(-, -, -)$
Step III, after pepsin digestion	4	2.5×10^8	$-(-, +\pm, +, \pm)$
Step III, after phosphomono- and phosphodi-esterase digestion	4	2.5×10^8	$+ \pm (+\pm\pm, -, +\pm, +\pm, +\pm)$
Step III, after heating (70°C x 10 min)	3	2.5×10^8	$+ \pm (+\pm\pm, -, -, +\pm)$
Step V	3	5×10^8	$+ \pm (+\pm\pm, \pm, +\pm)$
Placebo	6	—	$-(-, -, -, \pm?, -, -)$

*1 ml semen = about 10^8 spermatozoa. **As mean values (in brackets, the individual values).

complete cortical clarification of the crystalline lens (approximately 50% decrease). The nuclear opacity is usually unaffected.

Results

Table 1 summarises the clarification values obtained from 43 treated old dogs. An example of marked clarification of the cortical opacity is shown in Fig. 1. The latent period of the effect varies between 6 and 10 hours after the first injection; further clarification may appear after some days.

Tryptic and papain digestion, as well as hydrochloric acid hydrolysis, performed at purification step III, completely destroyed the activity. A lessening of the activity was observed after pepsin treatment. The activity was unaffected by heating at 70°C for 10 minutes in aqueous solution, and by calf intestine phosphomonoesterase and snake venom phosphodiesterase digestion. These experiments showed the presence in the active factor of peptide bonds, the splitting of which abolishes the biological activity.

Such activity cannot be detected in extracts of other tissues (kidney, tongue, heart, and brain), processed up to purification step III, or with glycine, sorbitol, or other pharmacologically inac-

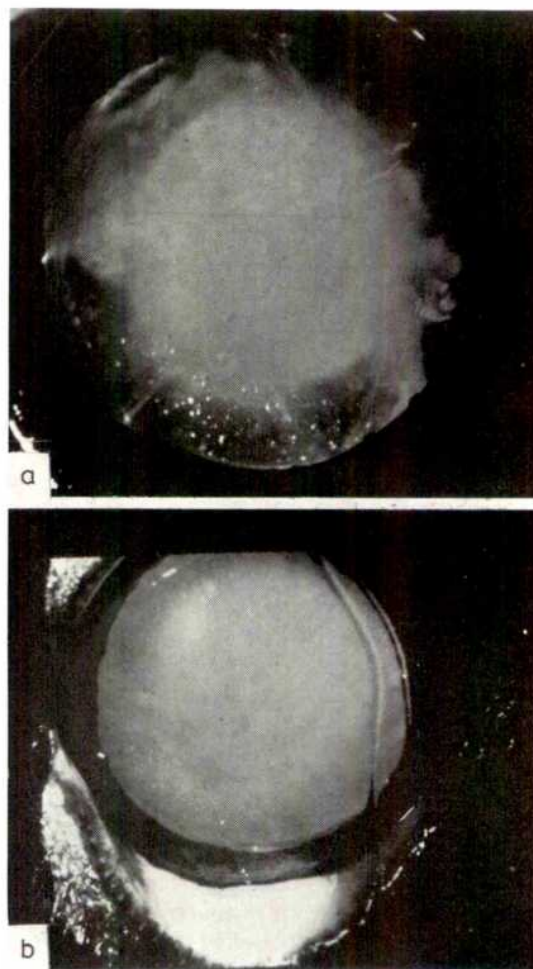


Fig. 1 Photobiomicroscopy of the crystalline lens opacified from senile cataract of dog no. 36 (13 years old, 12 kg bodyweight), before (B) and 24 hours after (A) the first treatment. Two intramuscular injections in 12 hours of purified gametic fraction III, each equivalent to 2.5×10^8 spermatozoa/kg, obtained as described in the text. The lowering of the cortical opacity appears to be uniform

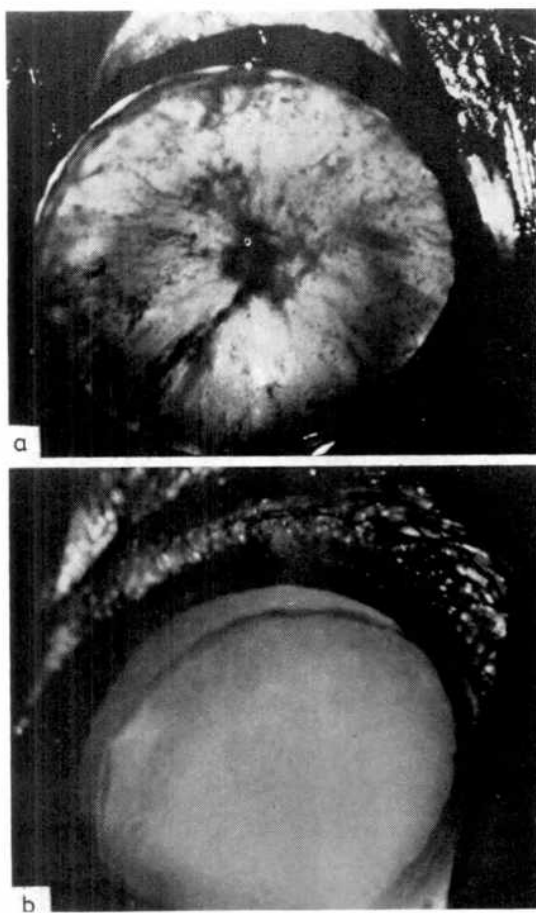


Fig. 2 Photobiomicroscopy of the crystalline lens opacified from senile cataract of dog no. 9 (12 years old, 11 kg bodyweight), before (B) and 24 hours after (A) the first treatment. Two intramuscular injections in 12 hours of purified gametic fraction step III, each equivalent to 2.5×10^8 spermatozoa/kg, obtained as described in the text. The total surface of the crystalline lens indeed appears to be fragmentary.

tive compounds (placebo). This biological activity is not specific for the crystalline lens. Positive responses may also be observed in the appearance of the skin and fur, the avidity of the appetite, the postural tonus, and the general alertness of the animal.

It is interesting to note that sometimes the nuclear and cortical opaque layers in the crystalline lens seemed to become divided into small fragments, with wide transparent spaces between them (Fig. 2).

Discussion

The phenomenon of partial remission of cataract in

the crystalline lens seems to be a specific one, as it follows the increase in specific activity during the purification stages from whole semen. We do not understand the mechanism of this temporary metabolic correction, possibly leading to a partial remission of the signs of senility. But it is worth recalling that similar remissions can be simultaneously observed in many biochemical functions which commonly undergo senile modifications—for example, the lipoproteidemic spectra^{7,8}—and more generally in conditions related to slowed-down cytodynamics such as delayed wound healing,⁹ repair of bone fractures,⁹ the induction of some hepatic enzymes (glucokinase, NADPH oxidase, tyrosine amino transferase, 5-aminolevulinic acid synthetase), the activity of which is lessened in senescence (Casellato *et al.*, in press). It is possible that the activity of this (these) principle(s) may concern protein synthesis, but it is not yet clear at what level.

Thus the absolute irreversibility generally thought to be inherent to some metabolic processes, such as senescence, may be questionable, for irreversibility may be partly mitigated by some such factor(s) acting as a homeostatic regulator(s).

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Intraocular implants: the postoperative astigmatism

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SUMMARY A series of 100 cases of intraocular implants has been considered, especially with regard to the postoperative astigmatism. This was found to be far higher than in a similar series of cases subjected to the same techniques without an implant. The operative results appear to be as good as in any conventional series, except for 2 cases. The reason for the excessive astigmatism (average 2.84 D) is not clear but the following factors have been suggested: (1) faulty surgical technique, that is, irregular corneal healing; (2) astigmatic errors in the actual intraocular lens itself; (3) tilting of the intraocular lens; (4) the intraocular lens, owing to its own inherent weight, may pull on the iris and ciliary body and even distort the cornea on healing. A summation of all these factors could produce an undesirably high degree of astigmatism.

Intraocular lens implantation has now become a widely accepted procedure and is being performed routinely by many surgeons in this country. While the long-term implications, if any, have not been assessed, it is possible to consider the advantages and disadvantages in the short term. The purpose of this study was to consider the amount of astigmatism in the final spectacle correction and note the differences in amount after routine cataract extraction without an implant.

In 1977 I considered^{1,2} the astigmatism in 328 cases, using different methods of section and suturing. One hundred intraocular implants have now been performed, and in all cases a corneal section with interrupted or continuous sutures was used. There was therefore a baseline for calculation for the postoperative astigmatism for either method, and any gross deviation from this would be noticeable. Implants have been inserted for over 20 years, and the following is mentioned only to record the actual method used rather than to add anything new to established principles.

Materials and methods

SURGICAL TECHNIQUE

The operating microscope and general anaesthesia were used in all cases. A half-thickness groove was made of nearly 170 degrees, an 8/0 black stitch was inserted at 12 o'clock, and converted into a loop. The anterior chamber was entered with a Bard-

Parker No. 11 blade and the section completed with scissors. Alpha-chymotrypsin was used in all cases and a peripheral iridectomy performed.

Delivery was with the intracapsular forceps rather than with a cryoprobe. Forceps delivery appears to have the definite advantage that the pupil need not be dilated preoperatively, and a small pupil makes insertion of the implant easier and safer.

The implant was held with the same intracapsular forceps, inserted diagonally with a backhand movement and without releasing, and the iris was lifted over the upper posterior loop. It was then adjusted into a vertical position.

Considerable care was taken over case selection. An implant was not proceeded with if vitreous bulge was produced when the cornea was lifted. This meant that there was no case of vitreous loss in the series.

Results

The visual acuity was 6/6 to 6/12 in 84 cases, 6/18 to 6/60 14 cases, and less than 6/60 2 cases. These visual results are as good as any series of conventional extraction, but as noted above there was definite case selection. There were 2 cases with resultant poor vision which could not have occurred had an implant not been inserted. One case had an iris prolapse causing shift of the implant, so that it touched the cornea, and the implant had to be removed. There was 1 case of severe corneal oedema which required a corneal graft. There was one postoperative retinal detachment, but the view of a

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single U-shaped tear was so good through the implant that repair of the detachment was straightforward, with good visual result.

POSTOPERATIVE ASTIGMATISM

It was soon apparent that the postoperative astigmatism was higher than in similar series without an implant in which the same method of sectioning and suturing was used.

In 1977 using four different methods I found postoperative astigmatism as follows:

Method	Sutures	Astigmatism	No. of cases
Conjunctival flap	Continuous	0.97 D	70
No flap	Continuous	1.27 D	100
Conjunctival flap	7 Direct	1.72 D	82
No flap	7 Direct	2.00 D	76

In this present series of 100 cases with implant the average was 2.84 D, that is, 3 times as much as the lowest figure above and nearly twice as much as the 2 methods used (nos. 2 or 4). There were 2 cases with +6.0 D, 3 cases of 5.5 D. None of these cases showed any evidence of corneal distortion. The sections had all healed normally and there was of course no vitreous loss for the reason as stated.

A scatter diagram (Fig. 1) was made which shows this position, and if the line of +2.0 D is taken it will be seen that there are many more cases above this figure. For easy comparison all the astigmatic

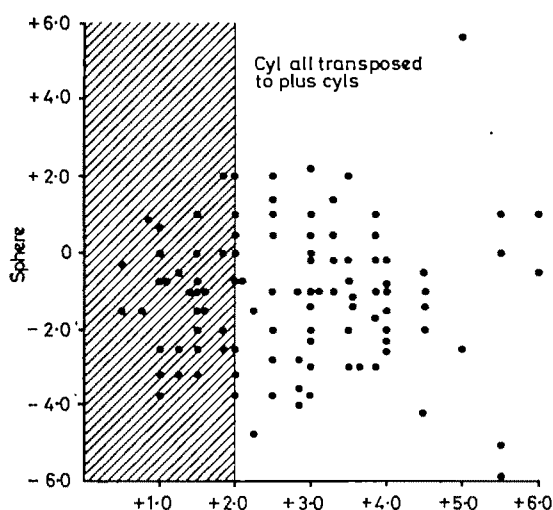


Fig. 1 Scatter diagram showing amount of astigmatism. Cylinders transposed to plus cylinders. Note (a) large numbers of cases above +2.0 D cyl; (b) tendency to shift to minus sphere.

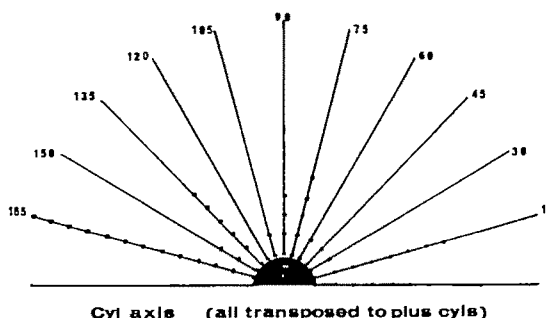


Fig. 2 Scatter diagram showing axis of cylinders. Note preponderance of axis being at 180 degrees.

values were converted to plus cylinders. It will also be seen that there is some shift to a minus sphere.

Fig. 2 shows the axis of the cylinders. These were again converted to plus cylinders and there is a clear preponderance to the axis being at 180 degrees.

POSSIBLE CAUSES OF EXCESSIVE POSTOPERATIVE ASTIGMATISM

This can be considered under three headings: (1) faulty surgical technique; (2) astigmatic error in the intraocular lens itself; (3) tilting of the intraocular lens.

In all cases the wound had healed satisfactorily. There was no case of vitreous loss. The manoeuvre of insertion of the implant is simple and does not distort the cornea. Indeed, if observation is made through the cornea while the anterior chamber is filled with saline, there is little raising of the cornea and far less than any 'open sky' technique.

There is always the possibility that different methods of section and suturing will influence the postoperative astigmatism. Percival and Yousef³ in a series of 25 cases of intraocular lens implants state that their results yielded only an average of less than 1.5 D, but this present series has attempted to compare a series of 100 intraocular implants with another series without implants by the same surgeon using the same techniques.

On the assumption that excessive astigmatism was not due to faulty surgical technique it was possible that the fault was in the intraocular lens itself. Two unused Binkhorst lenses were opened in their original ampoule as supplied by the manufacturer.

The intraocular lens was suspended by tapes in the centre of a blank trial lens. Unfortunately no clear image could be obtained with this with a focimeter because of its size, but it was found possible to assess the dioptric power with some accuracy by neutralisation.

The power of the intraocular lens as stated by the manufacturer was +19.0 D but this is of course the power in aqueous, and if measured in air the power is very much higher.

The power of the intraocular lens when suspended in air can be calculated as follows:

If n' is the refractive index of the intraocular material = 1.49,
 n'' is the refractive index of the aqueous = 1.336,
 F is the power of the lens in aqueous +19 D,
 r is the radius of curvature of the lens,

$$\text{then } F = \frac{n' - n''}{r}$$

$$\text{or } 19 = \frac{1.49 - 1.336}{r}$$

$$r = 8.11 \times 10^{-3}.$$

Then substituting r of 8.10 when lens is in air:

$$F = \frac{n' - 1}{r} \quad \text{or} \quad F = \frac{1.49 - 1}{8.10}$$

$$F (\text{power of intraocular lens in air}) = 60.5 \text{ D.}$$

It will be noted for ease of understanding that this calculation only refers to a simple plano-convex lens, ignoring its thickness.

It was found possible to neutralise this intraocular lens in air although it was of high power and there was a difference of power at 90 degrees. There was a measurement of 61.0 D along the 180 degree axis and 62.0 D along the 90 degree axis, giving a cylinder of 1.0 D at 180 degrees. There was therefore a +1.0 D cyl in the intraocular lens as tested, and if this had been used for an actual operation it would of course influence the necessary spectacle correction required. No firm conclusion can be drawn from this observation, however, as only 2 lenses were tested, and, in addition, as this observation was made in air the amount of astigmatism must be less as the lens will be suspended in aqueous.

With the kind help of M. Jalie, of the City and East London College, the same 2 lenses were measured on the optical bench. Both lenses were recorded as +19 D (in aqueous) by the manufacturers, and one was found to be BVP 62.34 D and the other 61.74 D (in air), but no noticeable astigmatism was recorded.

Tilting of the intraocular lens might well produce astigmatism. Binkhorst,⁴ considering the question of intraocular lens operation, says that the iris in an aphakic eye is an unstable membrane subject to

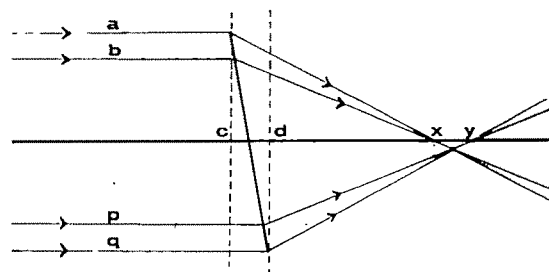
tilting movements (iridodonesis), and for this reason iris supported lenses are subject to displacement. Gravity and centrifugal forces exert their influence on the intraocular lens. Suturing of the upper loop to the iris could well produce a backwards tilt or, without a stitch, it might tilt forwards. The effect of tilting can be shown in the accompanying diagram (Fig. 3). Again this applies only to a very simple lens.

Assuming a thin lens, we find that a parallel beam AB at the top of the lens would come to a focus at X and a beam PQ at the bottom would come to a focus at Y where CX and DY would be equal and represent the focal length of the lens. There would therefore be an induced spherical aberration giving more than one focus and so a possible cylinder effect. It is appreciated that the formulae and diagrams are extremely simple and there may be other factors which could be taken into account.

The tilting of an intraocular lens has been considered in some detail by Jalie,⁵ and from his more detailed and more scientifically accurate calculation a tilt of 10 degrees in a lens of 16.62 D, which is an average power, would produce 0.48 D of astigmatism. The mathematics of the calculation are complicated and are set out in his paper.

Discussion

A considerable amount of detailed work has been done on the correct dioptric strength of the intraocular lens required so that the patient's postoperative vision is as near as possible to emmetropia. Based on the preoperative refraction and corneal curvature, various formulas have been considered. Many of these are highly theoretical and will probably be nullified by human factors such as irregular healing of the wound. For the same reason measurements of the axial length by ultrasound have the same disadvantages. There is probably no need to go further beyond the simple



Ray Diagram of a Tilted Spherical Lens

Fig. 3 Diagram showing passage of rays of light through a tilted lens (see text).

formula as suggested by Jaffe,⁶ namely, multiply the patient's preoperative refraction by 1.25 and add this to 18.00 D to obtain the dioptric power of the intraocular lens to be inserted.

The accuracy of the intraocular lens itself has been considered. McReynolds *et al.*⁷ has examined the intraocular lens at the time of operation in a lensometer during surgery and found that only 35% of lenses checked were found to have the exact power as indicated. They also found that some lenses had poor qualities of resolution when an image was viewed through them. This might be due to astigmatic error. The lenses tested in this paper did not show these gross inaccuracies.

Few authors have considered the possibility of this induced astigmatism, but Drews⁸ states that the average astigmatic error in various series is 2.5 D to 3 D. A highly accurate determination of lens implant power can be frustrating if the patient has a large postoperative astigmatic error. Control of corneal astigmatism presents a much more critical

problem in patients with lens implants than those who are simply fitted with cataract glasses.

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Anterior chamber depth in eyes with pseudoexfoliation

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SUMMARY The depth of the anterior chamber was measured in 34 eyes with pseudoexfoliation but without glaucoma and in 334 normal controls. No significant difference was found.

Angle-closure glaucoma is likely to develop in eyes with shallow anterior chambers and narrow angles.¹ Primary angle-closure glaucoma is thought to be rare and to occur by chance association in eyes with pseudoexfoliation.²⁻⁶ Glaucoma with pseudoexfoliation may, however, present with symptoms suggesting angle closure,⁷ have a high incidence of narrow angles⁸—perhaps caused by phospholipid iodide—or be associated with pupil block⁹ or iridocapsular block.^{10 11}

The anterior chamber depth is similar in eyes with primary open-angle glaucoma and glaucoma associated with pseudoexfoliation^{12 13} and in eyes with and without pseudoexfoliation¹⁴—in an admittedly small sample.

This paper presents the results of comparisons between the anterior chamber depths of non-glaucomatous eyes with and without pseudoexfoliation.

Material and methods

The anterior chamber depth of 334 normal eyes and 34 eyes with pseudoexfoliation was measured on a randomly chosen sample during an epidemiological survey of the Negroes of Pondoland, South Africa (this survey is fully reported by Bartholomew¹⁵). Measurements were made with the Goldmann pachymeter attached to the Haag-Streit slit-lamp on right eyes only and excluded those with glaucoma. The corneal thickness and the combined depth of cornea and anterior chamber were measured. The anterior chamber depth was then obtained by subtracting the corneal thickness from the combined measurement. The mean of 3 readings was recorded.

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Table 1 *Anterior chamber depths in 334 normal eyes without pseudoexfoliation by age and sex*

Age group	Males			Females			Significance levels	
	No.	Mean (mm)	SD	No.	Mean (mm)	SD	t	2P
40-49	44	2.74	0.29	44	2.61	0.24	2.17	<0.05
50-59	48	2.73	0.23	40	2.49	0.28	4.00	<0.001
60-69	39	2.61	0.30	36	2.52	0.29	1.32	>0.05
70+	44	2.60	0.32	39	2.51	0.32	1.31	>0.05

Table 2 *Anterior chamber depths in 158 normal eyes and 34 eyes with pseudoexfoliation*

	Pseudoexfoliation			Normal			Significance levels	
	No.	Mean (mm)	SD	No.	Mean (mm)	SD	t	2P
Males	17	2.58	0.36	83	2.60	0.30	0.21	>0.8
Females	17	2.46	0.32	75	2.51	0.30	0.59	>0.5

Results

The anterior chamber depths of the control sample are shown in Table 1.

There was a decrease in anterior chamber depth with increasing age for men ($t=2.15$, $P<0.05$) and for women ($t=1.6$, $P>0.05$). The chamber depth was greater in men than women for those between 40 and 59 years of age but was not significantly different in those over 60 years of age.

The anterior chamber depths in eyes with pseudoexfoliation were all measured in persons over 60 years of age and are shown separately for men and women in Table 2. The measurements are compared with those from controls over 60 years of age.

The observed differences were very small and not statistically significant.

Discussion

There was no significant difference in the depth of the anterior chamber of eyes with or without pseudoexfoliation. This confirmed the findings of Forsius *et al.*¹⁴ It is unlikely that eyes with pseudoexfoliation have the anatomical predisposition of a shallow anterior chamber, which is common in primary angle-closure glaucoma.

If angle closure does develop in association with pseudoexfoliation, some other mechanism must be responsible, as suggested by Herbst,⁹ Bartholomew,¹⁰ and Dark.¹¹

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Long-term follow-up study on prevention of aphakic cystoid macular oedema by topical indomethacin

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SUMMARY In addition to routine medications topical indomethacin was applied to one group of 112 eyes and an appropriate placebo was applied to another group of 106 eyes that underwent intracapsular cataract extraction. The investigation was conducted in a prospective double blind fashion over a long period of time in order to demonstrate the effects of indomethacin in preventing the development of cystoid macular oedema. Indomethacin drops were instilled once a day before surgery, twice on the day of surgery, and 3 times daily for 2 weeks postoperatively. The prevalence of cystoid macular oedema as detected by fluorescein angiograms was as follows: in the early period (from 1 to 2 postoperative months), cystoid macular oedema developed in 25% of the indomethacin-treated eyes and in 51% of the untreated eyes; in the middle period (from 4 to 7 postoperative months), it developed in 11% of the former group and 21% in the latter group; in the late period (from 1 to 1.5 postoperative years) it developed in 9% of the former group and 11% of the latter group. In both the early and middle periods the difference in prevalence was statistically significant, but in the late period there was no significant difference between the 2 groups. The onset of 'indomethacin-masked cystoid macular oedema' in several treated eyes may account for the insignificant difference in the late period. Prolonged biosynthesis of indomethacin-sensitive materials, including prostaglandins, may be suspected in some aphakic eyes.

There is no conclusive theory as to the aetiology of aphakic cystoid macular oedema. Hypotony,¹ inflammation,² and vitreous traction³ have been regarded as causes. However, causative factors still remain obscure.

Several investigators, including the authors, have pointed out that the occurrence of the disease is in some way related to the synthesis of prostaglandins (PGs) initiated by surgical trauma.^{4–6} Miyake⁵ postulated a hypothesis as follows. The main causative factors of cystoid macular oedema seem to be the release of PGs into the aqueous and other inflammatory mediators derived from a disrupted blood-aqueous barrier. These substances diffuse from the aqueous into the posterior pole of the fundus, where they increase the permeability of the perifoveolar retinal capillary plexus. Based on this hypothetical consideration, Miyake has shown that the incidence of cystoid macular oedema after intracapsular extraction of a senile cataract can be greatly reduced by pre- and postoperative

application of topical indomethacin.^{5,7} Having measured the amounts of PG-E and PG-F by radioimmunoassay techniques, Miyake *et al.*⁸ also demonstrated the suppressive effect of topical indomethacin on the synthesis of PGs during lens extraction. These reports originally stressed that indomethacin should be administered pre- and shortly postoperatively because PGs are synthesised most actively during the surgery and shortly after it. Therefore in general this mode of therapy is deemed to be prophylactic. Recently two double-blind studies were carried out to evaluate indomethacin administered systemically. One study failed to demonstrate the effect in preventing cystoid macular oedema at its usual dosage of 25 mg even given pre- and postoperatively,⁹ and the other noted a decrease in occurrence of the disease with excessively high dosage of 100 mg daily, which was given shortly after the operation.¹⁰ To date, however, all authors, including ourselves, have investigated the effect of indomethacin only in short-term follow-up studies.

In the present study the effect of topical indomethacin in preventing cystoid macular oedema was examined and compared with that of a placebo in

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Table 1 Age and sex distribution in the study population

	Indomethacin group	Control group
Age	65.99 $\pm$ 7.22	65.90 $\pm$ 8.14
	NS by <i>t</i> -test	
Sex	63 Females/49 males	59 Females/47 males
	NS by χ^2 -test	

a controlled, double blind, long-term follow-up study. The period of investigation was divided into 3 phases: early (from 1 to 2 postoperative months), middle (from 4 to 7 postoperative months), and late (from 1 to 1.5 postoperative years). This study was undertaken to define the clinical and aetiological significance of topical indomethacin in the treatment of aphakic cystoid macular oedema.

Material and methods

SUBJECTS

In the present study a total of 238 eyes underwent intracapsular lens extraction because of senile cataract and were randomly assigned to indomethacin or control group. We excluded the eyes from our study that had surgical accidents such as vitreous loss, rupture of the lens capsule, or endophthalmitis, and had other ocular conditions associated with cystoid macular oedema or other pre-existing macular diseases. Finally the study comprised 218 eyes. Fifty-four patients were operated on unilaterally and 81 bilaterally. Sixty-two patients were male and 73 female. They ranged in age from 57 to 92 years, with an average of 65.9 years. There was no statistically significant difference between the 2 groups in sex and age distribution (Table 1).

SURGICAL PROCEDURE

Surgery was performed by one of the authors (KM), using the same technique throughout. Retrobulbar anaesthesia and akinesia were induced with lignocaine. After a corneoscleral incision had been made with a razor blade the wound was enlarged with Troutman's corneoscleral scissors. Peripheral iridectomy was placed at the 12 o'clock position, and the lens was extracted by a sliding method, by means of a cyropencil and an irisretractor. In no cases was alpha-chymotripsin used, and zonulolysis was performed by gently pressing the scleral wound edge. The wound was closed with five interrupted 10-0 nylon sutures.

MEDICATIONS

Indomethacin powder (obtained from Merck-Banyu Co, Tokyo) was dissolved in sesame oil at a

concentration of 1% in slightly modified way as reported by Sawa and Masuda¹¹ and sterilised by boiling. For the control group only pure sesame oil sterilised by boiling was used. These 2 solutions were placed in separate vials of the same appearance. All these procedures were performed in the pharmacy of the hospital under the guidance of the controller (KM) of the study, who had access to the randomisation code. The solutions were given to the patients by one of the authors (HM) without knowledge of their components. Informed consent had been previously obtained from all the patients.

Indomethacin drops were instilled once the day before surgery, twice on the day of surgery (3 hours and 1 hour preoperatively), and 3 times daily for 2 weeks postoperatively.⁸ Pre- and postoperative medications, that is, local corticosteroids and systemic and local antibiotics, were given in a routine manner.

Pure sesame oil, together with routine medications, was administered to the control group in the same way.

DETECTION OF CYSTOID MACULAR OEDEMA

Fluorescein angiography was performed at each of the 3 stages of the investigation (early, from 1 to 2 months postoperatively; middle, from 4 to 7 months postoperatively; and late, from 1 to 1.5 years postoperatively). Some patients were unable for social or psychological reasons to attend all 3 angiography sessions. The severity of cystoid macular oedema was graded into 4 classes on the basis of fluorescein angiograms, biomicroscopic appearance, fundus drawings, visual acuity, and visual field. Details of the grading system were given previously^{5,7} and only brief remarks are made here.

Grade 0 has no symptoms and shows no trace of changes on the fluorescein angiogram. Grade I is the subclinical group in which slight fluorescein retention is seen on the angiogram, and the area of the retention is less than or equal to 1 mm². The lesion does not show a complete circle round the fovea. No abnormality can be detected by ophthalmoscopy or slit-lamp microscopy. Grade II is the group with objective symptoms, and the fluorescein angiogram shows the dye retention in the macular area forming a complete circle in stellate or flower petal pattern. The diameter of the lesion is less than 2 mm (4/3 disc diameter), that is, the area of the lesion is less than or equal to 3.14 mm² but larger than 1 mm². On ophthalmoscopy no marked changes can be seen, but biomicroscopy often reveals the presence of cystic oedema. No marked functional deterioration can be found in the visual

Table 2 Prevalence and severity of cystoid macular oedema in indomethacin-treated and untreated eyes

Follow-up postoperative period	Severity of diseases No. of eyes (%)									
	Indomethacin group					Control group				
	0	I	II	III	Total	0	I	II	III	Total
Early (1st-2nd mo.)	84 (75%)	21 (19%)	7 (6%)	0 (0%)	112 (100%)	52 (49%)	34 (32%)	18 (17%)	2 (2%)	106 (100%)
Middle (4th-7th mo.)	83 (89%)	7 (8%)	2 (2%)	1 (1%)	93 (100%)	74 (79%)	15 (16%)	4 (4%)	1 (1%)	94 (100%)
Late (12th-18th mo.)	80 (91%)	6 (7%)	2 (2%)	0 (0%)	88 (100%)	80 (89%)	6 (7%)	4 (4%)	0 (0%)	90 (100%)

acuity and the visual field. Grade III is the group with subjective symptoms, and in many cases attenuation of the visual acuity and central relative scotoma can be demonstrated. Fluorescein angiography shows fluorescein retention of a circular pattern with a diameter larger than 2 mm, that is, an area larger than 3.14 mm². Definite changes of the macular area can be seen by biomicroscopy and ophthalmoscopy. These changes may persist and lead to permanent disturbance.

An ophthalmic photographer and one of the authors (SS), who had no knowledge of the medications given, evaluated the severity of the disease.

Results

The prevalence and the severity of cystoid macular oedema, in both the indomethacin-treated and placebo groups, is shown in the Table 2. In the early period after surgery dye leakage was found in 51% of the control group and in 25% of the indomethacin group. The difference is statistically highly significant (χ^2 test, $P < 0.005$). In the middle period dye leakage was found in 21% of cases in the control group and in 11% of the treated group. The difference is statistically significant (χ^2 test, $P < 0.005$). During the middle period the prevalence of leakage decreased in both groups compared with the early period. During the late period the prevalence decreased further in both groups: dye leakage was found in 9% of cases in the indomethacin group and in 11% of cases in the control group. This difference is not statistically significant (χ^2 test, $0.05 < P < 0.25$).

Gradual decreases in macular leakage were recognised in the indomethacin group as well as in the control group, which agrees with the natural course of the disorder. The fact that the difference in prevalence of macular leakage between the treated and untreated eyes became statistically insignificant during the late postoperative phase is in part ascribed to the late onset of macular leakage

in several indomethacin-treated eyes. Among 8 treated eyes that showed macular leakage during the late phase 4 had late-onset macular leakage. On the other hand among 10 eyes of the control group that showed macular leakage during the late postoperative period none had late onset and 3 had middle onset. One case is reported here.

CASE REPORT

A 64-year-old woman with senile cataract underwent intracapsular lens extraction without pre- or post-operative complications. By the method described above indomethacin was given together with other usual medications. In fluorescein angiograms done 1.5 and 7 months postoperatively there was no trace of dye leakage in the macular area (Figs. 1 and 2). This eye had a visual acuity of 1.2 at both angiography sessions. In the 13th postoperative month

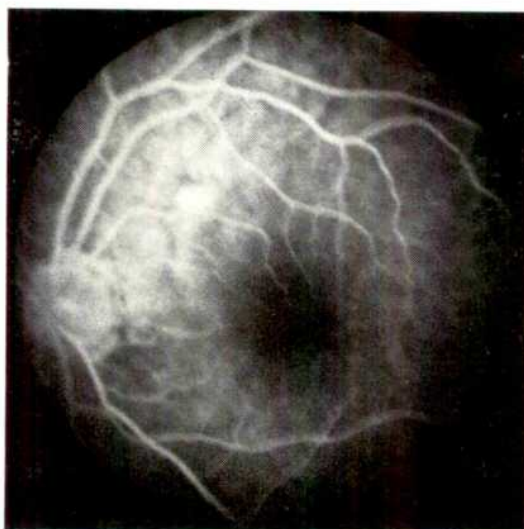


Fig. 1 Fluorescein angiogram of the reported case taken 1.5 months postoperatively. No trace of dye leakage is seen in the macular area

the patient complained of blurred vision. Fluorescein angiograms taken at that time revealed cystoid macular oedema of grade II (Fig. 3). Visual acuity at that time was 0.8.

When we evaluated the postoperative visual acuity, we excluded 15 eyes and 10 eyes from the indomethacin group and the control group respec-

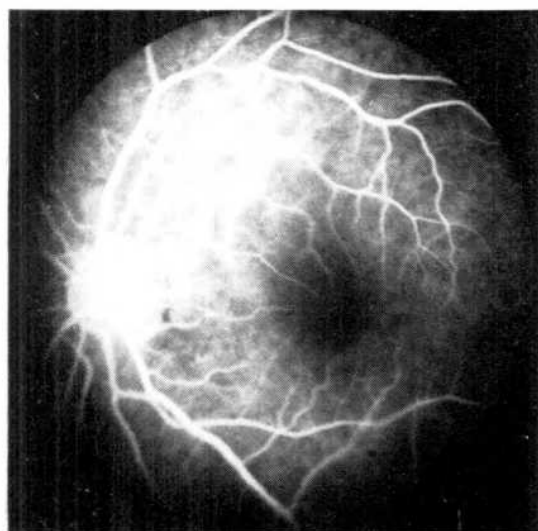


Fig. 2 Fluorescein angiogram of the reported case taken 7 months postoperatively. No trace of dye leakage is seen

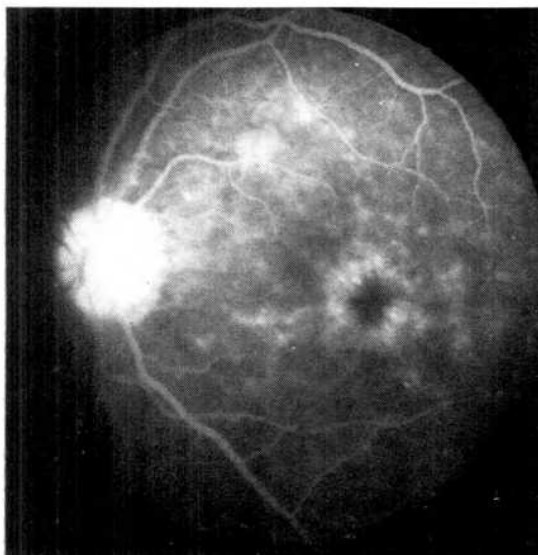


Fig. 3 Fluorescein angiogram of the reported case taken 13 months postoperatively. Note cystoid macular oedema of grade II

Table 3 Visual results

	Distributions of vision		No. of eyes (%)	
	Indomethacin group		Control group	
	1-0-0-0	0-3	1-0-0-0	0-3
Early period (1st-2nd mo.)	94 (98)	3 (2)	85 (89)	11 (11)
Middle period (4th-7th mo.)	82 (99)	1 (1)	87 (98)	2 (2)
Late period (12th-18th mo.)	82 (100)	0 (0)	82 (99)	1 (1)

tively. These eyes had optic disc atrophy, and a suspicion of amblyopia; also it was impossible to determine the exact visual acuity of these patients because of their poor health and low intelligence. In each postoperative period the distribution of visual acuity in the indomethacin group was significantly better than that in the control group ($P < 0.05$). In the other 2 periods there were no significant differences between the 2 groups.

Discussion

In the present study the natural course of cystoid macular oedema was compared in eyes treated with indomethacin and in untreated eyes following intracapsular cataract extractions. In the control group the incidence of the disease in the early postoperative period was 51%, and it decreased to 11% by the late postoperative period (4% of clinical cystoid macular oedema). This rate of incidence agrees with that reported by others.¹²⁻¹⁴ However, the incidence of cystoid macular oedema during the early postoperative period was less in this study than in previous studies.⁵⁻⁷

In both the indomethacin-treated and the untreated eyes this disorder was found to show a similar self-limiting tendency, that is, a high incidence during the early postoperative period and a gradual decrease thereafter.

The present study reconfirmed the finding that topical indomethacin reduced the occurrence of cystoid macular oedema during the early postoperative period. This study also demonstrated the prophylactic effect of indomethacin during the middle period. Furthermore, these findings suggest that the onset of cystoid macular oedema during the early and middle postoperative periods is closely related to the presence of indomethacin-sensitive substances (prostaglandins, for example) which are biosynthesised during the surgical procedure. Conversely, during the late postoperative period there was no difference in the incidence of

cystoid macular oedema between the 2 groups. One of the reasons for the low incidence of the disease during the late postoperative period is mathematical chance and another reason is the possibility of 'indomethacin-masked cystoid macular oedema', as shown by the case report. Such was the case in 4 of 8 eyes that had macular leakage during the late postoperative period. The number of cases of indomethacin-masked cystoid macular oedema was such that no significant difference was found between the 2 groups during the late postoperative period. In these eyes, which were aphakic, the synthesis of small amounts of indomethacin-sensitive substances (probably prostaglandins) may be abnormally prolonged.

In a case previously described¹⁷ cystoid macular oedema appearing 3 months after cataract surgery subsided on the application of indomethacin for 1 week and recurred when indomethacin therapy was withheld.

In some cases, elevated levels of prostaglandins E and F were observed not only during surgery but also after it.⁸ These phenomena, together with the results of the present study, indicate the abnormal condition of biosynthesis and extraocular removal of indomethacin-sensitive materials in aphakic eyes. The factors that influence this condition remain to be investigated. It has not been clearly shown which substances are sensitive to indomethacin. Among possible candidates are aqueous biotoxigenic complex (ABC factor),¹⁸ histamine, bradykinin, and 5-hydroxytryptamine.¹⁶ In view of previous investigations^{5, 7, 8, 17} we strongly suspect that prostaglandins are uniquely susceptible to the effects of indomethacin.

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HLA antigens in acute anterior uveitis in South African blacks

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SUMMARY Fifty-three black patients with acute nongranulomatous anterior uveitis (AAU) were tissue typed and the results compared to those from a panel of 200 healthy unrelated black volunteers. No statistically significant deviation from the norm with regard to the frequencies of 38 HLA antigens could be observed.

The striking association between HLA B27, acute anterior uveitis (AAU), certain rheumatic disorders like ankylosing spondylitis, Reiter's disease, reactive arthritis, and juvenile rheumatoid arthritis has been described by several authors and is well documented (Brewerton *et al.*, 1973a, b; Schlosstein *et al.*, 1973; Caffrey and James, 1973; Brewerton *et al.*, 1974; Rachelefsky *et al.*, 1974; Brewerton, 1975; Mapstone and Woodrow, 1975; Zervas *et al.*, 1977; Ohno *et al.*, 1977).

However, in several series of patients investigated for AAU there was a considerable number of patients who possessed the antigen HLA B27 but did not show rheumatic or any other systemic disorders, the percentages of this type of patient ranging from 30% to 45%. The frequency of the antigen in the relevant control groups ranged from 4% to 8% (Brewerton and colleagues, 1974; Mapstone and Woodrow, 1975; Zervas *et al.*, 1977; Brewerton and James, 1975). All these investigations were undertaken in white patients, in whom it is now generally accepted that idiopathic AAU, that is, without rheumatic or other obvious systemic diseases, shows a significant association with the antigen HLA B27.

Perkins (1976) observed the absence of AAU due to rheumatic conditions in immigrant negroes from West Africa living in London and related this finding to the reported absence of HLA B27 in this ethnic group. Ayanru (1977) also reported the rarity of acute nongranulomatous anterior uveitis associated with rheumatic diseases among Nigerian patients and attributed this to the absence of the genetic

marker HLA B27 among Africans. In his series most of the cases showed posterior uveitis, anterior uveitis being relatively rare.

In contrast Freedman (1974) observed a different distribution in South African blacks, as most of his 355 cases suffered from anterior uveitis, and posterior uveitis was seen far less commonly. Furthermore the rate for anterior uveitis among the South African blacks, 24 per 100 000, was significantly higher than the rate of 12 per 100 000 found in Rochester. During his investigation into the aetiology of uveitis in Bantu adults Freedman (1976) observed 2 patients out of 311 in whom ankylosing spondylitis was the associated disease and described these patients as being unique, ankylosing spondylitis being extremely rare among South African blacks (Baum and Ziff, 1970).

Though the antigen HLA B27 is not altogether absent in South African blacks, it does occur at a very low frequency of 0.6% to 0.7% (Hammond *et al.*, 1977; David *et al.*, 1979). It is completely absent in the normal healthy Japanese population (Tsuji and Fukunishi, 1973). Yet when Sonozaki *et al.* (1975) investigated 27 Japanese patients who presented with ankylosing spondylitis they found the antigen present in 67% of their cases.

It was of interest, therefore, to investigate whether the association of HLA B27 and AAU, with or without systemic disease, as reported in white populations, would also hold true for a black population group.

Patients and methods

PATIENTS

Fifty-three black patients suffering from acute non-

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granulomatous anterior uveitis were chosen for this study out of hundreds of uveitis cases seen at the St John's Eye Hospital, Baragwanath, during the years 1976 and 1978. All the patients were examined by 2 of the authors (B.M. and J.F.), and the particulars were recorded indicating history, age, sex, clinical description of the disease, and results of laboratory investigations. Diagnosis was based on clinical symptoms such as pain, photophobia, lacrimation, and recurrence, and signs such as circumcorneal injection, keratic precipitates (not mutton fat), cells and flare in the anterior chamber, and increased intraocular pressure.

All the patients underwent the routine battery of investigations adopted for uveitis which includes: x-rays of the chest, sinuses, and sacroiliac joints, full blood count, erythrocyte sedimentation rate, anti-streptolysin titre, blood sugar level, gonococcal complement fixation test, toxoplasma dye and complement fixation tests, serum protein electrophoresis, fluorescent treponemal antibody test, Rose latex test for arthritis, and a delayed hypersensitivity skin test for tuberculosis. The control panel consisted of 200 healthy unrelated black volunteers belonging to various Southern African tribes.

HLA TYPING

Tissue typing was performed at the Tissue Bank of the South African Institute for Medical Research in Johannesburg. The method used was the Standard 2 Stage NIH Lymphocyte Microcytotoxicity test at an incubation temperature of 37°C throughout the test, trypan blue as the indicator dye. A total of 174 different typing sera were used to identify 38 HLA antigens: 17 of the A locus, 18 of the B locus, and 3 of the C locus. Although the first group of 16 patients were investigated in 1976 and the remaining patients in 1978, the range of antisera remained essentially the same. The exception was the introduction of antisera against Aw30, Aw31, and Aw33. For the typing of the first group only antisera with the specificity Aw30/Aw31 were available, whereas for the 1978 group antisera which allowed differentiation between Aw30 and Aw31 and later on Aw33 were at the typing team's disposal. The statistical evaluation of the results was performed by employing the χ^2 test with Yates's correction.

Results

There were 28 males and 25 females among the patients. The mean age of the males was 35.3 years and that of the females was 31.1 years.

Twenty of the patients, on questioning, reported previous episodes of ocular symptoms which might from the patients' descriptions have been attacks of

Table 1 HLA antigen frequencies in black patients with acute anterior uveitis (AAU)

	Controls No. = 200 %	AAU patients No. = 53 %	χ^2	P
HLA-A1	7.0	13.2	1.38	NS
Aw36	0.5	3.8	1.54	NS
A2	26.0	17.0	1.40	NS
A3	10.0	11.3	0.0007	NS
A9	18.0	18.9	0.0029	NS
A10	0.0	0.0	—	—
Aw25	0.5	1.9	0.199	NS
Aw26	14.5	17.0	0.054	NS
Aw34	9.0	1.9	2.11	NS
A11	0.5	3.8	1.54	NS
A28	20.0	32.1	2.84	NS
A29	12.0	17.0	0.529	NS
Aw30	27.0	13.2*	2.358	NS
Aw31	15.0	5.4*	1.71	NS
Aw32	4.0	3.8	0.10	NS
Aw33	4.3 ¹	8.7 ²	0.155	NS
Aw43	0.5	1.9	0.0199	NS
HLA-B5	4.5	1.9	0.222	NS
B7	20.0	26.4	0.68	NS
Bw42	20.0	11.3	1.58	NS
B8	8.0	5.7	0.079	NS
B12	24.0	17.0	0.948	NS
B13	1.0	1.9	0.0336	NS
B14	6.0	3.8	0.0855	NS
B15	2.5	3.8	0.001	NS
B17	34.0	39.6	0.3604	NS
B18	14.0	11.3	0.0795	NS
B27	1.0	5.7	2.60	NS
B37	0.0	1.9	0.51	NS
B40	2.0	1.9	0.252	NS
Bw16	2.0	3.8	0.06	NS
Bw21	1.0	1.9	0.0336	NS
Bw22	2.5	3.8	0.001	NS
Bw35	11.0	17.0	0.8932	NS
Bw41	1.0	2.7 ³	0.0025	NS
HLA-Cw2	36.0	21.6*	2.279	NS
Cw3	18.5	18.9	0.0188	NS
Cw4	25.0	34.0	1.286	NS

¹Tested 62. ²Tested 37. ³Tested 23.

acute anterior uveitis. None of the 53 patients had any overt clinical evidence of rheumatic or other systemic disease. Ten patients had a raised ESR, 6 had a positive serological test for syphilis, 3 had a positive test for toxoplasmosis, 3 had a raised antistreptolysin titre, 1 had active sinusitis radiologically, and 5 had a positive skin test for tuberculosis but no evidence of active tuberculosis.

None of the 3 HLA B27 carriers, 2 males and 1 female, showed any of the above clinical findings.

The frequencies of 38 HLA antigens in 53 black South African patients suffering from acute, non-granulomatous anterior uveitis, as compared to 200 controls, are presented in Table 1.

Discussion

The antigen HLA B27 was represented slightly more frequently in the patient group (3/53) than in the control group (2/200). However, this did not reach statistically significant proportions. None of the

remaining antigens showed any statistically significant deviation from the norm.

Antigen frequencies of the A, B, and C locus of the major histocompatibility complex of man vary between different racial groups (Payne *et al.*, 1977). The same applies to the linkage disequilibria which have been found to exist between these antigens (Ward and Biegel, 1976; Hammond *et al.*, 1977). Positive or negative linkage disequilibria occur when antigens of the different HLA loci are found together more frequently, or less frequently, on the same chromosome than would be expected by the frequency of the single antigen alone in a given population group. The association of HLA B27 or any other HLA antigen with a certain disease has been attributed tentatively to the location, on the genome, of specific immune response (Ir) genes in close proximity to the gene coding for HLA B27, or to the indicated HLA antigen, and to the occurrence of positive linkage disequilibria between these HLA markers and the, in man as yet, hypothetical Ir genes (Brewerton and James, 1975; Dausset and Hors, 1975; Svejgaard *et al.*, 1975).

Should this hypothesis be true, it is conceivable that the linkage disequilibria found in one racial group are not repeated in another racial group, consistent with the established racial variations in linkage disequilibria between antigens of the A, B, and C locus. This could be one reason why this study has not revealed an association between AAU and any of the HLA antigens in a group of 53 black patients. In this connection it is interesting to mention the well documented association of HLA B17 with psoriasis in whites (Russel *et al.*, 1972; White *et al.*, 1972). B17 is the antigen with the highest frequency, 33%–41%, on the B locus in blacks (Payne *et al.*, 1977; Hammond *et al.*, 1977; David *et al.*, 1979). Yet psoriasis is hardly present in the blacks of South Africa.

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Immunocompetence and transfer factor therapy in uveitis

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SUMMARY A study of the clinical course of 20 patients with uveitis treated with transfer factor is reported. Twelve (60%) of the patients were initially immunoincompetent on screening. Eight of the 12 changed to an immunocompetent status after treatment and could either decrease or discontinue their anti-inflammatory drugs. Five had a statistically significant improvement in visual acuity. One of the 8 initially immunocompetent patients had a statistically significant visual improvement, and 2 decreased or discontinued all drugs, while 3 increased their drugs.

In 1949 Lawrence¹ demonstrated that delayed hypersensitivity to tuberculin can be transferred from sensitive to nonsensitive individuals by injecting leucocytes. It was later shown that a subcellular fraction of lysed leucocytes can also accomplish passive transfer of delayed hypersensitivity. This fraction was obtained by dialysing the lysed leucocytes, and therefore consisted of molecules smaller than 10 000 in molecular weight. It was designated as transfer factor. This substance is capable of improving cellular immune responses and has been used clinically in diseases in which demonstrable defects exist in the cellular immunity.² Therapeutic benefits have been reported in immunodeficiency diseases, malignancies, and viral illnesses.^{3–14}

In addition to improvement in cellular immunity the possible mechanisms of action may include induction of interferon.^{15,16}

Wolf *et al.*¹⁷ found that transfer factor therapy was effective in alleviating the mucocutaneous and articular manifestations of Behçet's syndrome in 4 of 6 patients, while Frenkel *et al.*¹⁸ found the maintenance oral steroid dosage could be tapered in a patient with severe Behçet's disease after transfer factor treatment. Kozun *et al.*¹⁹ found that transfer factor, while mitigating the mucocutaneous lesions and fever of neuro-Behçet's disease, had no demonstrable effect on the neurological findings. Transfer factor was also found to be effective in herpetic keratoconjunctivitis.⁷

This study was undertaken to assess the effect of transfer factor treatment in uveitis.

Materials and methods

Between January 1975 and June 1978, 20 of the patients with uveitis seen in the eye department of Southwestern Medical School were studied. They were referred because they were not responding to treatment with anti-inflammatory drugs, including local or systemic corticosteroids. In some of the patients corticosteroids were inducing lens changes or glaucoma. The patients were seen at consecutive visits to the eye department, an average of 6 times before transfer factor therapy and 16 times after the start of treatment.

There were 20 patients in the study, 8 were males, 16 were Caucasian, 3 Latin American, and 1 black. The ages ranged from 7 to 74 years with an average of 29.3 years. Sixteen patients had binocular disease and 4 unocular. The patients were followed up for 2 to 27 months, the average being 18.5 months. The duration of disease at the time of initiation of the study varied from 1 month to 16 years, the average duration being 5 years.

Informed consent was obtained from the patients. Each patient had a visual acuity assessment with correction and with a pinhole if on mydriatics as indicated. The anterior segment was examined with a slit-lamp, and an anterior chamber count and vitreous cell count was done with the room darkened and with 10 times magnification and a 0.3 mm slit-lamp beam. When the cell count was recorded as a range, the mean value was determined. The average

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Table 1 Visual acuities and anterior chamber cell and vitreous cell numbers before and after transfer factor treatment

Patient	Before treatment					After treatment										
	Visual acuity				Anterior chamber cells		Vitreous cells		Visual acuity				Anterior chamber cells		Vitreous cells	
	RE	LE			RE	LE	RE	LE	RE	LE	RE	LE	RE	LE	RE	LE
1	6/24	20/80	6/15	20/50	9	10			6/12	20/40	6/12	20/40	1	2		
2	6/60	20/200		20/600					6/60	20/200		20/500				
3	6/90	20/300	6/90	20/300	2	1				20/500		20/500	0	0		
4			6/18	20/60							6/18	20/60				
5	6/60	20/200	NPL		1		30		6/60	20/200	NPL		4		26	
6	6/60	20/200	6/9	20/30	7	29	8		6/15	20/50	6/6	20/20	8	5	3	
7			6/60	20/200		5		9			6/18	20/60	11			15
8	6/12	20/40	6/12	20/40	3	19	4	8	6/9	20/30	6/15	20/50	11	10	6	4
9	6/120	20/400		20/500	4	1	0	15	6/30	20/100	6/60	20/200	0	0	20	3
10	6/21	20/70	6/30	20/100	20	20			6/15	20/50	6/21	20/70	18	19		
11	6/60	20/200	6/90	20/300	3	4	6	7	6/30	20/100	6/60	20/200	8	3	13	14
12			6/18	20/60		5		20			6/15	20/50		4		12
13	6/30	20/100	6/21	20/70	8	7	10	10	6/21	20/70	6/9	20/30	4	4	3	7
14		20/600		20/500					6/120	20/400	6/60	20/200				
15	6/75	20/25			3				6/9	20/30			3			
16	6/21	20/70	6/24	20/80	11	1	1	1		20/90	6/18	20/60	0	0	0	0
17	6/5	20/15	6/5	20/15	11	1	1	1	6/6	20/20	6/6	20/20	0	0	0	0
18		20/200	6/30	20/100					6/18	20/60	6/6	20/20				
19	6/12	20/40	6/6	20/20	9	14	7	3	6/12	20/40	6/6	20/20	8	7	3	3
20				20/500		19						20/600		14		

visual acuity, anterior chamber cell count, and vitreous cell counts before and after transfer factor treatment were recorded (Table 1). Gaps in the table are due to nonavailability of data. All patients were maintained on anti-inflammatory drugs and/or steroids locally, subconjunctivally, or systemically as was required throughout the trial.

The fundus was examined with direct ophthalmoscopy, indirect ophthalmoscopy, Hruby lens, and Goldmann 3-mirror lens. Where indicated fluorescein angiography was done and retinal and internist opinions sought. Investigations were tapered according to the clinical nature of the uveitis. A complete blood count, erythrocyte sedimentation rate, test for lupus cells, and human leucocyte antigen typing were done as indicated. Serology for syphilis and toxoplasmosis, including fluorescent antibody tests, histoplasmosis, coccidiomycosis, and antistreptolysin O titre were also

done when indicated. Serum albumin-globulin ratio, serum calcium, purified protein derivative skin tests, antinuclear factor, x-rays of skull, chest, hands, and lumbosacral and sacroiliac joints were tests done when appropriate.

Clinically 9 patients had panuveitis, 4 had anterior uveitis, 2 had posterior uveitis, the remaining 5 having peripheral uveitis, choroidoretinitis, iridocyclitis, retinal oedema and iritis (Table 2). The diagnosis was unknown in 9 cases. The diagnosis was presumed as toxoplasmosis in 2 patients; Vogt-Koyanagi-Harada syndrome, ankylosing spondylitis, sclerosing keratitis in association, syphilis, Reiter's syndrome, and histoplasmosis in 6 others; and probably placoid pigment epitheliopathy, heterochromic cyclitis, and Harada's disease in the remaining 3 patients (Table 2). The patient with Harada's disease had bilateral exudative detachments but no cerebrospinal fluid pleocytosis.

Table 2 Sex, age, race, clinical appearance, and presumed aetiology of uveitis; immune status, immune and visual response on transfer factor

Patient	Sex	Age	Race	Clinical appearance	Presumed aetiology	Immune status	Response	
							Immune	Visual acuity
1	M	36	C	Iritis	Unknown	Abnormal	+	+ **
2	F	57	C	Retinal oedema	Histoplasmosis	Abnormal	++	(+)
3	F	34	C	Panuveitis	Syphilis	Normal		-
4	M	10	C	Posterior uveitis	Cong. toxoplasmosis	Abnormal	+	No change
5	M	54	C	Panuveitis	Unknown	Abnormal	-	-
6	F	13	C	Anterior uveitis	Unknown	Abnormal	++	+
7	F	7	B	Panuveitis	Unknown	Abnormal	-	+ *
8	F	38	C	Iridocyclitis	Unknown	Normal		(+)
9	M	7	C	Choroidoretinitis	?Placoid, pig. epith.	Abnormal	-	+ *
10	M	5	C	Anterior uveitis	Sclerosing keratitis	Normal		++
11	F	37	C	Panuveitis	Unknown	Normal		++ *
12	M	13	C	Anterior uveitis	?Heterochromic cyclitis	Normal		++
13	F	20	C	Peripheral uveitis	Unknown	Abnormal	+	+ **
14	F	24	LA	Panuveitis	Haradas's disease	Normal		+
15	M	37	LA	Anterior uveitis	Ankylosing spondylitis	Abnormal	++	-
16	F	74	C	Posterior uveitis	Unknown	Abnormal	+	(+)
17	F	20	C	Panuveitis	Unknown	Borderline	-	-
18	F	33	C	Panuveitis	Toxoplasmosis	Abnormal	±	+ **
19	F	36	LA	Panuveitis	?Haradas's disease	Normal		-
20	M	31	C	Panuveitis	Reiter's syndrome	Normal		-

(+) Indicates visual acuity improved in 1 eye and deteriorated in fellow eye. *P < 0.01, **P < 0.05. C = Caucasian, B = Black, LA = Latin America.

The patients underwent immunological evaluation at Wadley Institute of Molecular Medicine before transfer factor administration, 24 hours after the first dose of transfer factor, and at 3–6-monthly intervals. The immune studies included delayed hypersensitivity skin reactions to mumps, histoplasmin, candida, purified protein derivative, and streptokinase-streptodornase. These tests were read at 24 and 48 hours. The maximum of the 2 reactions was recorded.⁵

The percentage of E-rosette forming cells (T lymphocytes) was calculated in the peripheral blood as described previously.⁵ The E-rosette scores were also determined. This method gives semiquantitative information about the E-rosette receptors on lymphocytes. The transformation of lymphocytes in response to phytohaemagglutinin and pokeweed mitogen was calculated by measuring the incorporation of tritiated thymidine.²⁰

The test for B cell function included the determina-

tion of erythrocyte-antibody-complement (EAC) rosette-forming B cells²¹ and serum immunoglobulin levels. The immunoglobulins were determined by the standard radioimmunodiffusion technique. Lymphocyte transformation response to pokeweed mitogen also represents a B cell function.

The patients were randomised into 2 groups. One group received transfer factor in 5 units/m² once a week for 4 weeks and then every 2 weeks. The interval between injections was increased gradually, in some cases every 3 months if there was clinical improvement. The second group served as a control for the first 4 weeks and received a placebo injection at the same frequency. At the end of the first 4 weeks the code was broken. The patients who were receiving transfer factor were continued on transfer factor and those on placebo were started on transfer factor beginning with weekly injections. As a result of randomisation 5 patients fell into the placebo group and 15 into the transfer factor group.

Table 3 *Enhanced immune responses with transfer factor therapy*

Patient	% T cells		T cell score		Phytohaemagglutinin Blastogenic index		Pokeweed mitogen Blastogenic index	
	Pre-treatment	During treatment	Pre-treatment	During treatment	Pre-treatment	During treatment	Pre-treatment	During treatment
1	51	63	82	133				
2	50	60	90	110				
4					1.1	46.3	4.7	27.2
5			136	159	4.7	5.6	9.7	10.3
6	47	61	88	141				
7					1.8	3.2	2.1	6.9
13					1.6	15.6		
15					1.7	12.3	4.2	9.9
16	29	59	51	134				
18					0	2.8		
Normal	64 ± 6		128 ± 12		> 10		> 10	
Mean ±	SD							

The transfer factor was prepared from healthy household contacts of the patients, who were between the ages of 18 and 30 years.^{4,5} The donors were tested for their immunological status and also screened for hepatitis B antigen. The donors had to fulfil all the criteria for blood donation. Lymphocytes were collected with the aid of a continuous-flow centrifuge (Cell-trifuge-Aminco). This procedure yielded about 10^{10} lymphocytes on the average. One unit of transfer factor was the amount of transfer factor which was obtained from 10^6 lymphocytes. One donation of lymphapheresis, therefore, yielded 100 units of transfer factor. The data were analysed by the Student's *t* test.

Results

Eleven of the 20 patients had an abnormal immune status, while one had a borderline abnormal immune status resulting in 12 (60%) of the patients having defective immunity (Table 2). Tests for B cell function were within normal range except for impaired response to pokeweed mitogen, which is given in Table 3.

Retesting for immunocompetence showed that 8 of 12 patients (67%) showed improvement in immune status after transfer factor treatment. One patient had a borderline response and 3 remained incompetent.

Seven of the immunoincompetent patients had uveitis of unknown aetiology. Two had toxoplasmosis. The remaining 3 had presumed histoplas-

mosis, placoid pigment epitheliopathy, and ankylosing spondylitis (Table 2). Out of the 12 immunoincompetent patients 8 improved their visual acuity after receiving transfer factor (2 cases in one eye only), and of these 8 who improved 6 showed an improved immune status (Table 2).

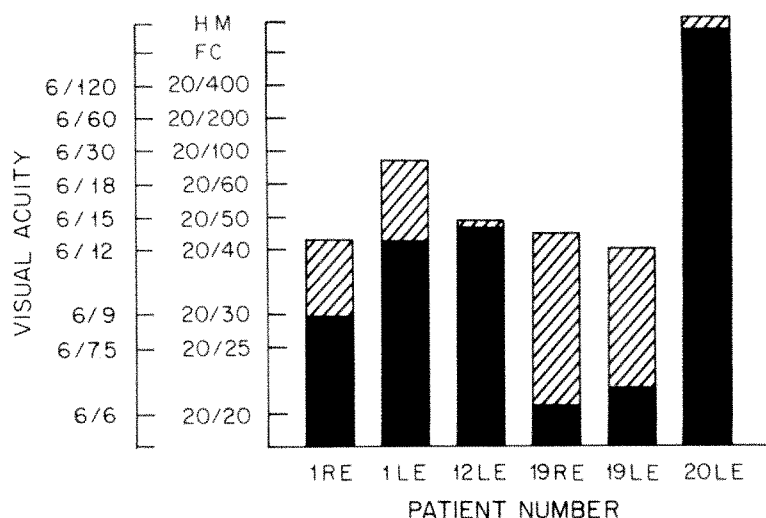
Seven of 20 patients (35%) improved their visual acuity, having less anterior chamber and vitreous cells. Four of these 7 had impaired immunity.

Ten (50%) of the patients in the study improved their visual acuity, and a further 3 improved the visual acuity in only one of their affected eyes. The average age for those improving their visual acuity was 19.7 years, the range being 5–37 years. Five of the 10 patients had uveitis of unknown cause, while the remainder had Harada's disease, posterior multifocal placoid pigment epitheliopathy, heterochromic cyclitis, and toxoplasmosis, and 1 was associated with sclerosing keratitis.

Six of the patients had a statistically significant improvement in their visual acuity (Table 2). Five of these had abnormal immunity and in 4 of these the cause of the uveitis was unknown.

There was no change in the visual acuity of 3 patients, while 4 patients suffering from syphilis, Reiter's syndrome, ankylosing spondylitis, and uveitis of unknown aetiology had a deterioration of visual acuity. Of these 4 patients who deteriorated 2 had normal immunocompetence, 1 had abnormal immune responses, and 1 had borderline immunocompetence, with change to normal immune responses.

Fig. 1 Visual acuities of patients on placebo treatment, cross-hatched areas included; and visual acuity on transfer factor treatment, cross-hatched areas excluded. (HM = hand movements, FC = finger counting)



Of the 5 patients who were given placebos initially 4 had better visual acuity and fewer cells after transfer factor treatment than they had before and after the placebo were given (Fig. 1).

Concomitant treatment with the anti-inflammatory drugs, salicylates and indomethacin, and with systemic or subconjunctival steroid could be discontinued completely in 10 patients, namely, patients 1, 4, 6, 8, 9, 12, 13, 16, 17, and 18, and had to be increased in 3 patients, 10, 14, and 19, there being no change in the remaining 7 patients.

Table 3 shows those patients who had abnormality in their T lymphocytes either in the form of a low percentage of T cells (E-rosette forming cells) or diminished lymphocyte transformation in response to phytohaemagglutinin stimulation. Results of lymphocyte transformation in response to pokeweed mitogen, which is a B cell mitogen, are also included in this Table. The normal values for our laboratory are given at the bottom of the Table. If a value was decreased by more than 2 standard deviations, or less than 10 in case of lymphocyte blastogenesis, it was considered as abnormal. The patient numbers correspond to the patient numbers in Table 2.

The patients listed in Table 3 showed improvement in their T cell function. There was also improvement in the pokeweed mitogen blastogenic index. There was no definite relationship between the improvement in the immunological parameter and the significant improvement in uveitis. Six out of the 11 patients who showed statistically significant clinical improvement were those that showed improvement in the immunological parameters.

Eight of the patients had a normal immune screen. Five of these had panuveitis, 2 had anterior uveitis,

and 1 had iridocyclitis. Presumed aetiological diagnoses included Reiter's syndrome, associated sclerosing keratitis, syphilis, Harada's syndrome, probable Harada's syndrome and heterochromic cyclitis, and was unknown in 2 patients. Five of these immunocompetent patients improved their visual acuity, the improvement being statistically significant in 1 patient.

Discussion

It is interesting to note that 12 patients (60%) in this study had impaired immune status in the form of low E-rosette forming T lymphocytes or decreased lymphocyte blastogenesis. Nine of these (75%) showed improvement in the immune responses after transfer factor treatment. The immune responses improved in 8 of these patients to the extent that they were within normal range. Out of the 12 patients with impaired immunity, 7 had uveitis of unknown aetiology. It is possible that certain viruses were aetiological factors in these patients. Transfer factor could be effective through 2 different mechanisms if such is the case. The improvement in cellular immunity would be beneficial in eliminating the viral illness. The transfer factor has also been shown to induce interferon, which is an antiviral substance.^{15,16} Uveitis is also thought to be an autoimmune disease. Suppressor cell dysfunction has been associated with autoimmune problems. Transfer factor may also have a modulating effect on the suppressor helper cells relationship.

Transfer factor has beneficial effects other than improvement in cellular immunity. For example, it is capable of inducing interferon. Clinical benefits in patients with normal immune responses may occur

as a result of interferon induction or other, as yet unknown, effects of this substance.

Certain types of uveitis, such as phacoanaphylactic uveitis and sympathetic uveitis,²² are thought to be due to the liberation into the circulation of sequestered antigens. It is thought that the antigen antibody reaction initiates the uveitic process and that an anaphylactic process or Arthus-like reaction prolongs the process. It has further been postulated that either a change in the antigen or a modification in the susceptibility of the immunological apparatus to antigens tolerated thus far may be the basis for autoimmune disease.

Eight of the 12 initially deficient patients improved their visual acuity on transfer factor treatment, and 6 of these had also changed to an improved immune status. This clinical correlate suggests that the transfer factor may improve the uveitis by enhancing the patient's immunity, thus decreasing the actual uveitic process. Possibly suppressor T lymphocytes decrease cytotoxic antibodies and decrease B lymphocyte antibody production.

Ten of the 20 patients who improved their visual acuity in each affected eye had an age range of 5-37 years, the average age being 19.7 years, compared to the series average age of 29.3 years. It appears that the improvement in the uveitis, as monitored by visual acuity changes, occurs in younger patients.

The cellular immunity reaches its peak at about 16 years of age and undergoes a decline after the age of 35. The improvement in younger patients may also have resulted from the fact that they have an immune system more susceptible to enhancement.

Studies of the graphs of the visual acuity response on each patient indicate that the response occurs between 7 and 10 days after the initial injection of transfer factor and the course is then a step-like improvement. In patient 9, in whom transfer factor had been stopped and then resumed, this temporal effect is clearly seen (Fig. 2).

The use of anti-inflammatory drugs and local and systemic corticosteroids could be decreased or discontinued in some cases once transfer factor injection had commenced. In the 10 patients in whom these drugs could be stopped 8 had abnormal immunity initially. Of the 3 patients requiring increased medication all had normal immunity at the onset.

Patients receiving transfer factor for the Wiskott-Aldrich syndrome have developed autoimmune haemolytic anaemia or lymphomas. A direct relationship between the development of these complications and transfer factor cannot be established, since patients with this syndrome are prone to develop these complications. It has also been sug-

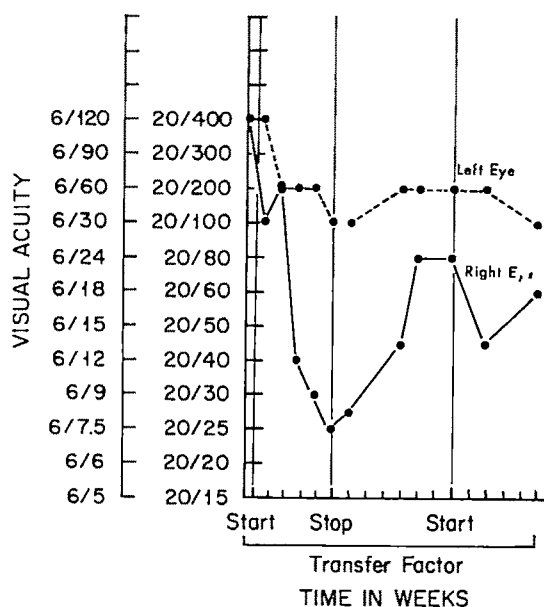


Fig. 2 Effect of starting, stopping, and restarting transfer factor on visual acuity of patient 9.

gested recently that patients with B cell defects develop haemolytic anaemia. Increases in immunoglobulin levels have been observed in patients with B cell diseases. One patient also developed hepatitis on transfer factor treatment. Side effects attributable to transfer factor were not observed in our study except for the complaint of pain at the site of the injection. However, in view of the possible suggestion of side effects, one should observe and monitor patients closely if B cell defects exist.

As this pilot study does not have a matched control group and the series is small, no definite conclusion can be arrived at. The clinical correlation between immunoincompetent uveitis, change to immunocompetence with transfer factor treatment, and the improved visual acuity while decreasing anti-inflammatory and steroid drugs treatment suggests it may at present be reasonable for a trial of transfer factor treatment primarily in severe uveitis in immunoincompetent patients when the cause is unknown.

We thank Robin Hill, Carolyn Michnoff, and Cynthia Benjamin for their technical assistance.

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Experience with the CAM vision stimulator: preliminary report

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A. WILLIAMS, AND L. DEAN

*From the Orthoptic Departments of the Birmingham and Midland Eye Hospital
and the Birmingham Children's Hospital*

SUMMARY Eighty-four children with at least 2 lines of amblyopia were treated with the CAM vision stimulator. 91% of the children who had received no previous amblyopia therapy showed improvement, 73% achieving 6/12 vision or better. Of children in whom previous occlusion therapy had failed 73.8% improved. The treatment appears to be effective, rapid, and well tolerated. Our initial impressions have been sufficiently favourable to stimulate further clinical evaluation.

Amblyopia probably affects between 4%¹ and 7%² of children in this country. Our understanding of the pathophysiology of amblyopia has blossomed over the last 20 years,³⁻⁵ yet the treatment has remained essentially unchanged since 1746.⁶ Occlusion continues to be the mainstay of treatment, and though it is recognised to be both psychologically and educationally disruptive, alternative methods have not as yet proved sufficiently effective to supplant it.⁷ Recent reports of experience with a new, physiologically based, form of treatment have been encouraging.^{8,9} We report an independent, preliminary assessment of this treatment.

Materials and methods

Children attending the Orthoptic Departments of the Birmingham and Midland Eye Hospital and the Birmingham Children's Hospital were included in the study if they had 2 or more lines of amblyopia—as measured by linear optotypes—and were able to co-operate with treatment. All children had a full ophthalmological examination, and no child with anterior segment or fundus pathology commensurate with the visual acuity was included.

All the children were refracted under cyclopentolate cycloplegia, and full optical correction was prescribed. When the spectacles had been worn for at least 1 week, treatment was started. Each child was shown a series of high-contrast square-wave gratings of different spatial frequencies, and treat-

ment was undertaken with the 3 smallest discernible gratings. Each in turn was rotated at 1 revolution per minute behind a clear Perspex cover on which the child drew or played pencil games under supervision. The session lasted 7 minutes and was repeated at weekly intervals for 4 weeks. If the visual acuity was still improving after 4 weeks, further weekly sessions were arranged. Otherwise treatment was discontinued at this stage.

The children had a full orthoptic examination at the beginning and end of treatment, and the visual acuity was measured before and after each session. Four weeks after treatment had been discontinued the children had a further orthoptic examination.

Between sessions the children received no additional treatment.

Results

Eighty-four children were included in the study. Their ages ranged from 3 years 4 months to 14 years 6 months with a mean of 6 years 7 months. Sixty-one children (72.6%) had received previous amblyopia therapy in the form of either part-time or full-time occlusion. The remaining 23 (27.4%) were 'new' cases.

Sixty-two of the 84 (73.8%) have attended for assessment 1 month after treatment was discontinued. Of the remainder 16 are continuing their treatment, and 6 have failed to attend for review.

The results are displayed in Figs. 1 and 2. The diagonal line in each case represents the 'no improvement' line, with improvement being recorded above the line and deterioration below.

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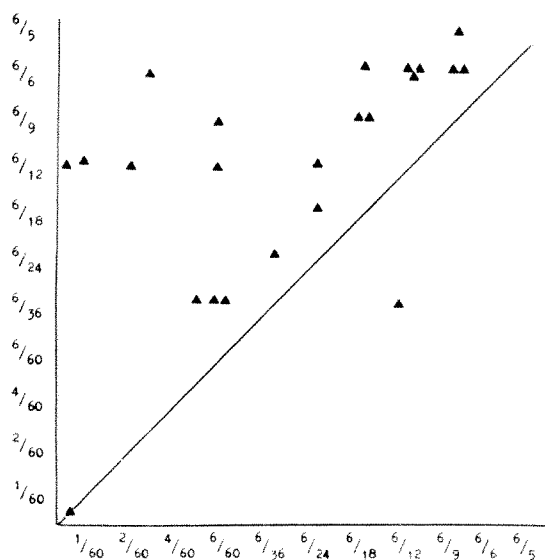


Fig. 1 Previously untreated patients: visual acuity at 6 m.

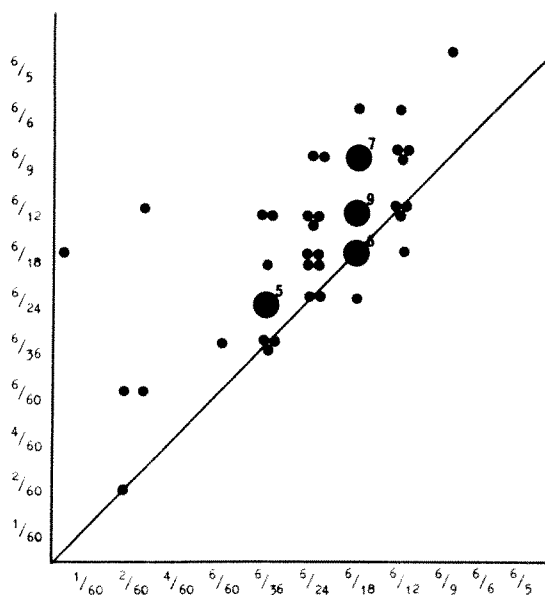


Fig. 2 Previously treated patients: visual acuity at 6 m.

The results in children who had received no previous treatment are examined separately (Fig. 1). In 21 (91%) the vision improved, in 1 the vision was unchanged, and in 1 there was considerable deterioration (6/12 to 6/36 in 4 weeks). Eleven of the 21 achieved their improvement in 4 weeks, 2 required 5 weeks, 3 required 6, 3 required 7, 2 required 8, and 1 child required 9 weeks. All the

children who failed to achieve N5 vision initially showed improved near vision, including the girl whose distance vision deteriorated.

Among the 61 children with previous occlusion 14 failed to improve and 2 deteriorated. The 45 (73.8%) children who improved showed generally more modest improvements, though there were some dramatic exceptions (Fig. 2). In 38 of the 61 only 4 treatment sessions were necessary, and in no case was more than 10 sessions needed. In all but 1 of these 'failed occlusion' children the near vision improved if it was not initially N5.

Fifteen previously untreated patients have been reviewed 4 weeks after the completion of treatment. Six have failed to maintain their visual improvement, but in only 2 was the regression more than 1 Snellen line, and neither of these have regressed to their pretreatment vision.

Forty-seven previously treated patients have also been followed up for 4 weeks after completion of treatment, and 18 (38.3%) have failed to maintain their improvement. Indeed 15 of these 18 have reverted to their 'pre-CAM' vision within the 4-week follow-up period.

In this group there were no instances of diplopia, no increase in the angle of squint, and no failures of attendance during treatment.

Discussion

In children receiving amblyopia treatment for the first time the results are promising. 91% showed improvement in their distance vision, 73% achieving 6/12 or better, 1 child from an initial vision of 1/60. These improvements were frequently obtained within 4 weeks and appear to be well maintained.¹⁰ The disturbance to normal education is limited, and there is no social embarrassment for the child, both factors of great importance in this age group. The good patient acceptance is mirrored by the 100% treatment completion rate.

In children who have had previous occlusion our results are similar to those originally reported,⁸ with 73.8% showing an improvement. Again these improvements were achieved much more rapidly than one would anticipate with occlusion,¹¹ with, therefore, less disruption to normal life. However, in our children these results were not well maintained, with almost 40% reverting to their pre-treatment vision. None the less, a maintained improvement in 60% of children with failed occlusion must still be regarded as encouraging.

The potential for this form of treatment is enormous, and it is important that extensive clinical experience is obtained before exploring this potential. It appears to offer a rapid, inexpensive, and

successful form of treatment, with high patient acceptance and minimal social disruption.

Many features need further examination, including the optimum number and frequency of treatments, long-term maintenance of visual improvement, etc., and further studies will clarify these points. Our initial impression, however, is that the CAM vision stimulator may eventually replace occlusion as the first choice treatment of amblyopia.

We thank the Birmingham ophthalmologists for allowing us to examine their patients, Miss J. Kempster for help in refracting the children, and Mrs P. Brooks for her secretarial help.

THE CAM vision stimulator was kindly supplied by Clement Clarke International Ltd.

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A pilot study of children with amblyopia treated by the gratings method

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SUMMARY A total of 6 patients, 2 with anisometropic, 2 with strabismic and anisometropic, and 2 with strabismic amblyopia treated with the 'gratings method' showed more than 2 lines of improvement in linear visual acuity. Patient attention and interest and repeated testing of the visual acuity were uncontrolled factors in this study. Moreover, the detailed visual tasks performed by the amblyopic eye may in themselves be the reason for improvement. Clearly a careful study which controls these possibilities is needed before a claim can be made that the 'gratings' per se offer an improved method of treatment of amblyopia.

Great interest was aroused by the reports from Addenbrooke's Hospital and the Physiological Laboratory, University of Cambridge, of a new treatment for amblyopia.¹⁻⁴ We carried out a pilot study, without controls, of 30 children with amblyopia who were treated by this method. Twenty of these patients had had a poor response to treatment by conventional occlusion methods (group A) and 10 were previously untreated amblyopes (group B).

Patients and methods

Our study tried to follow as exactly as possible the method described by the Cambridge group. Visual acuity was tested at distance and near by rows and single optotypes with the refractive error corrected. Glasses, if needed, were worn for a minimum of 1 month before treatment was started. The initial visual acuity was recorded by one examiner and the final visual acuity by a different examiner who had no knowledge of the initial response.

Treatment consisted of viewing an apparatus on which any one of a range of high contrast, sharp-edged gratings were slowly rotated at 1 revolution per minute (r.p.m.) behind a transparent cover on which drawing games were played to ensure the child's attention to the stimulus.^{2,3} The nonamblyopic eye was occluded only during the actual treatment sessions.

Each child was given 5 treatment sessions of 7 to 14 minutes, and then progress was assessed. Five

sessions were chosen because the initial reports indicated that 'those who respond well to this treatment usually do so within the first two or three treatments'.¹ The longest interval between treatment sessions was 2 weeks, and then only because illness prevented 3 children from following the weekly schedule.

Overall we studied 30 patients (17 male, 13 female) with an age range of 3 years 2 months to 9 years. Twelve patients had amblyopia of the right eye and 18 had amblyopia of the left eye.

Results

Eight of the 30 patients gave unreliable responses and so were excluded from the series. The remaining 22 patients included 16 (group A) who had had previous treatment for amblyopia and 6 (group B) who had not.

Table 1 shows the types of amblyopia treated in each group and Tables 2 and 3 analyse the results in group A and group B respectively.

A total of 6 patients, 2 with anisometropic, 2 with strabismic and anisometropic, and 2 with strabismic amblyopia treated with the gratings method showed more than 2 lines of improvement in linear visual acuity. Surprisingly, 4 of these patients were in group A and 2 in group B.

Discussion

Many variables exist in testing visual acuity in children. The reliability of responses depends on their understanding of the test and on the amount

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Table 1 Amblyopia types and treatment

Types of amblyopia	Group A	Group B	Total no of patients
	Previous treatment	No previous treatment	
Strabismic (S)	6 (37.5%)	2 (33.33%)	8 (36.36%)
Strabismic + anisometropic (SA)	8 (50%)	1 (16.67%)	9 (40.91%)
Anisometropic (A)	2 (12.5%)	3 (50%)	5 (22.73%)
Totals	16	6	22

Table 2 Analysis of results: group A, patients who had previous treatment

Age of patient	Type of amblyopia	Fixation	Pre-treatment visual acuity	Post-treatment visual acuity	No. of lines improved
6 7/12	S	Eccentric	6/18	6/15	1
5 4/12	S	Central	6/21	6/21	0
5 8/12	S	Central	6/15	6/15	0
7 3/12	S	Central	6/18	6/18	0
5 1/12	S	Eccentric	<6/60	6/30	1*
8	S	Eccentric	6/60	6/18	3
4 3/12	SA	Central	6/15	6/15	0
7 4/12	SA	Central	6/12	6/9	1
7 4/12	SA	Central	6/18	6/9	3
4 2/12	SA	Central	6/21	6/12	4
8 11/12	SA	Central	6/15	6/7.5	2
3 11/12	SA	Central	6/60	6/60	0
7 2/12	SA	Central	6/12	6/12	0
7	SA	Central	6/60	6/60	0
4 2/12	A	Central	6/24	6/9	4
9	A	Central	6/60	6/60	0

*Treatment continuing. S = Strabismic amblyopia. SA = Strabismic + anisometropic amblyopia.

of interest it arouses. Better attention alone may account for several lines of improvement, as may familiarity with the test. It is hard to separate improved visual acuity from better testing conditions, increased ability to co-operate with the test, or from learning. For this reason an improved response of 2 lines or less on testing linear visual acuity was not considered adequate proof of improvement in visual acuity. It can be seen from Tables 2 and 3 that only 6 patients improved more than 2 lines with the 'gratings method', 4 in group A and 2 in group B. Two of these patients had

Table 3 Analysis of results: group B, patients who had not had previous treatment

Age of patient	Type of amblyopia	Fixation	Pre-treatment visual acuity	Post-treatment visual acuity	No. of lines improved
7 9/12	S	Central	6/18	6/9	3
5 10/12	S	Central	6/30	6/30	0
5 10/12	SA	Eccentric	6/60	6/60	0*
5 11/12	A	Central	6/60	6/60	0
7 4/12	A	Central	6/15	6/12	1
5 10/12	A	Central	6/18	6/9	3

*Improving with occlusion.

strabismic amblyopia, 1 patient in each group. Two had strabismic and anisometropic amblyopia, both in group A. The other 2 patients had anisometropic amblyopia, 1 patient in each group.

Reviewing the results of this pilot study has raised many points which require further investigation in a properly controlled series. For example, one 4-year-old child had a recurrence of strabismic and anisometropic amblyopia after occlusion therapy was stopped. Gratings treatment was tried with a good response (4 lines), but within 1 month of stopping treatment the visual acuity again relapsed. We have used 15 minutes per week occlusion combined with fine visual tasks for the past month, and visual acuity is again improving. Perhaps one of the things we shall learn from the gratings method is that considerably less occlusion than previously thought (provided it is combined with fine visual tasks) is needed to maintain optimum visual acuity during the developmental period. This would be a re-emphasis of statements that have appeared for many years,⁶⁻⁷ including the recent papers from Cambridge.

Anisometropic amblyopes were treated after they had worn their correction for at least 1 month. Could their continued improvement be due, at least in part, to improvement obtained simply by wearing their glasses?

Conclusion

It would appear from this pilot uncontrolled study that there are sufficient grounds for a properly controlled study to evaluate whether the gratings per se offer any advantages over conventional occlusion combined with detailed visual task work for the amblyopic eye.

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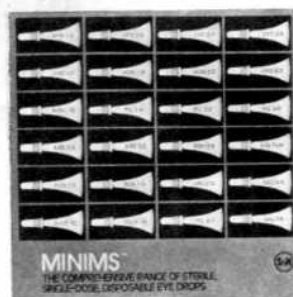
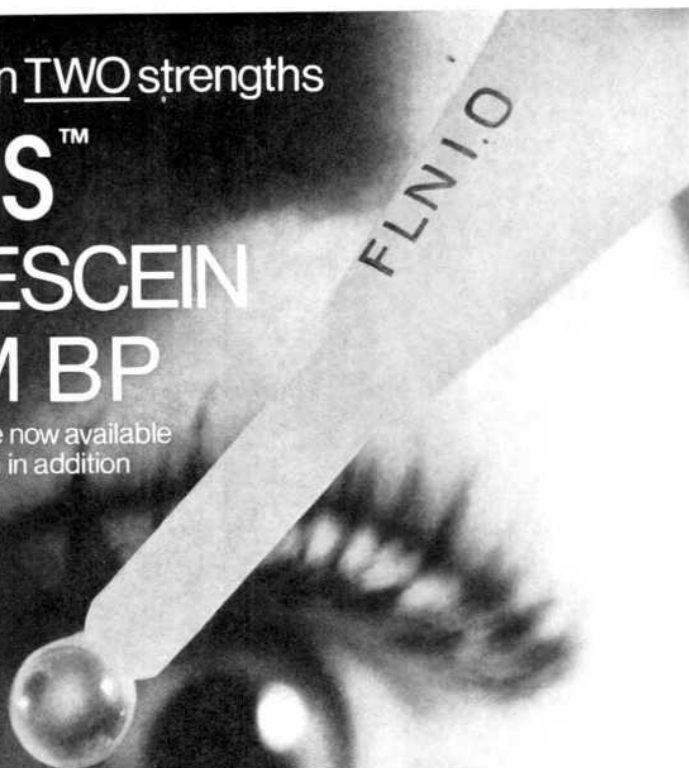
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A model for sensory adaptations of the visual system in squint

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SUMMARY Sensory adaptations to squint are considered in the light of present knowledge of the visual sensory system. A model to assist our understanding of the clinical presentation of sensory adaptation is proposed. Suppression and abnormal correspondence are considered as anomalies of different parts of the sensory system, and the interplay of these adaptations is reviewed.

In squint the embarrassment to binocular vision is considered to be of 2 types—diplopia and confusion. The object of regard has a central image in the fixing eye and a peripheral image falling on a non-corresponding area in the deviated eye. The object will therefore be located in 2 visual directions unless sensory adaptations occur. The location of the same object in 2 visual directions is diplopia. Confusion arises because in normal surroundings the fovea of the deviated eye will receive an image of some other object. If normal correspondence exists, the foveal image in the straight eye will be confused by this different foveal image from the deviated eye. Sensory adaptations occur to eliminate the diplopia and confusion. These adaptations are amblyopia, abnormal retinal correspondence, and suppression. The faulty pursuit of tracking movement that occurs in squint also may be due to the sensory adaptations.

Our understanding of the clinical presentation of these sensory adaptations has improved as new methods of investigation have been developed.¹ The purpose of this paper is to further our general understanding of these conditions by presenting a simple model of the visual system from the evidence of more recent advances in electrophysiology. Such a model must necessarily be a great simplification, as a large proportion of the physiological evidence is not derived from human subjects but from a variety of different animals. Only broad generalisations can be made, and it would be inappropriate to be too specific about the details of the human visual system.

It has become clear that the nerve fibres from the retinal ganglion cells to the centres of the brain are

of more than one type: those carrying the sustained response to a visual stimulus, the x cell system, and those carrying a transient response, the y cell system.² The former seems to be associated with central form vision and acuity, while the y system seems to be associated with the peripheral retina and concerned with the location of objects in space which enables fixation movements to be made. The x (sustained) system is concerned with *what* the object is, and the y (transient) system with *where* it is. For the purpose of this model the x system will therefore be referred to as the 'what system', and the more peripheral mechanism as the 'where system'.

There is also a deal of accumulated evidence for a third type of nerve cell associated with the central retina, the w cell. The likely purpose of this seems to be in serving the pursuit eye movements, retaining a central image when the eye is following a moving object.³ In line with the other 2 systems, this w mechanism will be briefly called the 'pursuit system'.

Fig. 1 is a schematic representation of the 'what' and 'where' systems. Three receptor cells are shown in association with 3 ganglion cells. To avoid confusion of the diagram the retinal bipolar cells are not actually drawn. These may connect more than 1 receptor to a ganglion cell. This lateral conduction across the retina, by which receptor cells from a receptive area are associated with 1 ganglion cell, is mediated also by horizontal and amacrine cells. This will be called 'confluence' of nerve paths, and is represented in the diagram by 1 horizontal cell. For a particular receptor the laterally conducting cells may allow confluence on more than 1 ganglion cell, so that a single receptor could send signals to be used by the visual system in different ways.⁴

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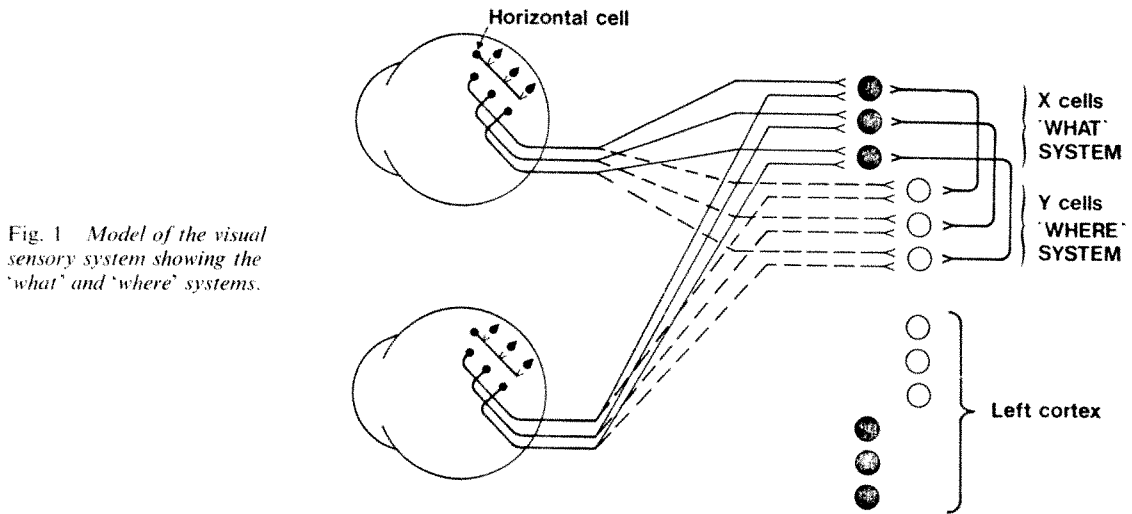


Fig. 1 Model of the visual sensory system showing the 'what' and 'where' systems.

It is suggested that the nerve impulses from the ganglion cell layer are mediated by the visual pathways to 2 brain centres.⁵ (Schneider 1969). This is represented in the diagram by the division of the nerve fibres to the 2 groups of cells labelled 'what system' and 'where system'. The diagram is not intended to indicate the actual anatomical details of the human system, which is still speculative. In some animals there is evidence to suggest that the 'what system' is the visual cortex in the occipital lobes and the 'where system' is in the superior colliculus of the midbrain,^{6,7} the 'where system' fibres leaving the visual pathway by the superior brachium just before the lateral geniculate body. In animals with forward-looking eyes and overlapping binocular vision, it appears likely that the visual cortex is also intimately concerned with the 'where system'.² However, the model is not concerned with precise anatomical detail but with giving a working understanding of the visual system to help our understanding of sensory adaptation to squint.

There is evidence to suggest that association fibres connect the likely locations of the 'where' and the 'what' system,⁸ and these fibres are represented in the right upper part of the diagram. The cortical cells are shown as circles and receive fibres from both eyes, that is, they are binocularly driven cells. In the diagram they represent the simplest level of cortical cell. In order that form vision can be elaborated a number of these simple cells are connected to a single more complex cell, and a number of these to a hypercomplex cell^{9,10} (Fig. 2). This further confluence (not shown in Fig. 1) occurs in the 'what system', and it results in the receptive area for the hypercomplex cortical cells being very

much larger than the retinal area connected to a single ganglion cell. In the process of form analysis, by the hypercomplex cells, the precise location of the image of the retina is lost, but localisation is not the concern of the 'what system'.

This is the simple model of the system. If we consider the sensory adaptations in terms of this dual system, we get a better insight into their nature

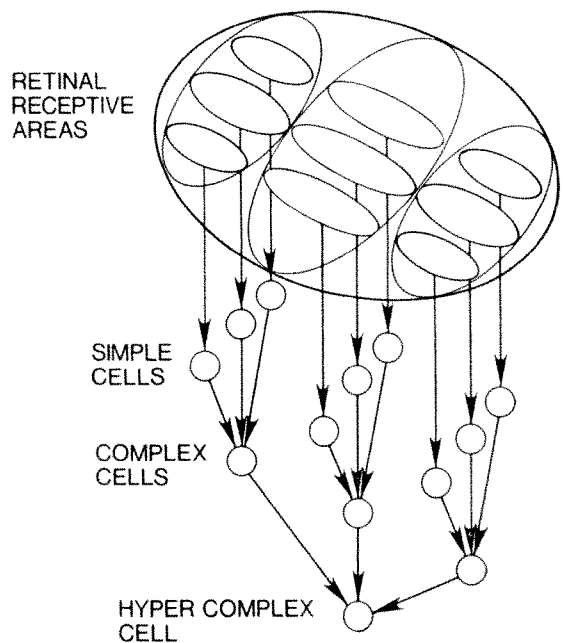


Fig. 2 Simple, complex, and hypercomplex cortical cells indicating the increase in retinal receptive areas with confluence of nerve paths.

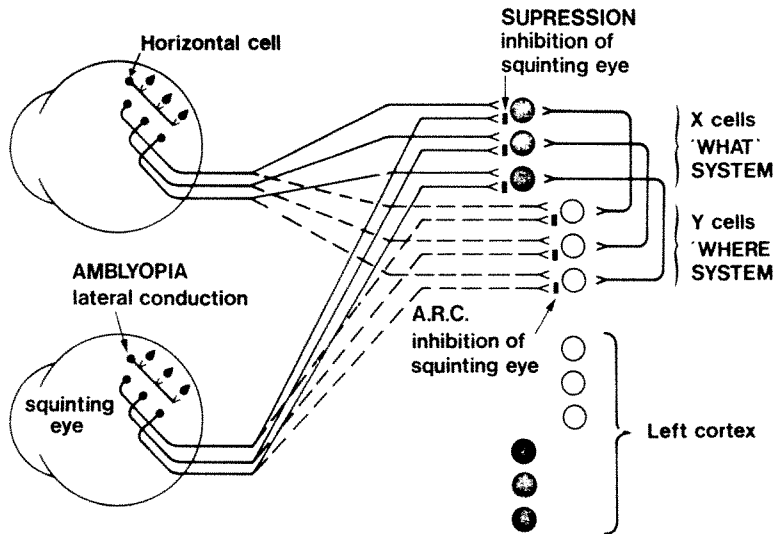


Fig. 3 Possible sites of abnormal confluence or inhibition which could account for sensory adaptations to squint.

than if they are considered in terms of a single visual pathway as previously.

Amblyopia

It has already been suggested that amblyopia can be explained in terms of an increase in lateral conduction.¹¹ A loss of acuity and form vision would occur if the 3 retinal receptors shown in Fig. 1 were to be connected to only 1 ganglion cell, or alternatively, if they were each connected to all 3 ganglion cells, which then sent the same signal to the associated cortex cells. This increased and abnormal confluence of nerve paths could occur in the retina and be mediated by the horizontal or amacrine cells as shown in Fig. 3, or it could occur at some higher point in the visual pathway. Although for simplicity of drawing the nerve fibres for both the 'what' and the 'where' systems are shown as coming from the same ganglion cells, they could, in fact, be separate ganglion cells for the 2 systems. If this were true, or if the confluence occurred at a higher point in the pathway, the confluence could affect the 'what system' and reduce acuity without the involvement of the 'where system'. This would permit amblyopia with no other sensory adaptations, which we know occurs frequently.

Suppression

In addition to a change in the degree of confluence occurring in the system another modification can occur—that of inhibition of a signal at a nerve synapse. Confluence and inhibition are both im-

portant aspects of normal sensory nerve processing, and their possible role in sensory adaptations has already been discussed.¹² It is now suggested that abnormal inhibition can occur separately in that 'what' and the 'where' systems (Fig. 3). If there is inhibition of the 'what system' fibres from the squinting eye, this would result in suppression of form vision from that eye. This is represented in Fig. 3 by the black rectangles interposed at the synapse between the x cell fibres from the squinting eye and the 'what system' cortical cells. The 'where system' could remain undisturbed. This would result in a squinting patient being unable to 'see' an object with the deviated eye, that is, no diplopia, but still being able to locate its direction.

This can be demonstrated clinically. If a patient with a large-angle squint (over 15°) is asked to look at a spot-light, this will be fixed with the dominant eye and the patient will report no second image. Where there is established suppression, no diplopia will be reported even if a red filter is placed before the straight eye and a green filter before the squinting eye. The patient will report that the green light cannot be seen. If the patient is then asked to turn the eyes to look at the green light, very many patients will be able to make a prompt and precise fixation movement to fix with the squinting eye. That is, the patient has turned the eyes to fix an object with the squinting eye even though this object could not be 'seen'. The 'what system' has been inhibited, but the 'where system' is still functioning. This seems to indicate the nature of suppression as an inhibition in the 'what system' which may leave the 'where system' intact. I believe that this is what occurs in squints with angles greater than

about 12° . In such convergent deviations the retinal image of the squinting eye lies more peripherally than the disc area.

Abnormal retinal correspondence

In abnormal retinal correspondence the inhibition is in the nerve fibres from the 'y' ganglion cells of the squinting eye (Fig. 3). This would mean that the image can be detected with the 'what system' from both eyes, but the only information regarding its visual direction comes from the 'where system' of the undeviated eye. The image in the deviated eye is therefore given the visual direction determined by the 'where system' of the dominant eye. The 'what system' of the deviated eye is able to detect the form of the image (within the limits of its acuity), but owing to normal confluence in image analysing process the exact location of the image is unimportant within certain limits. These limits appear to be about 12° , as suppression is more likely than anomalous correspondence if the angle of squint is greater than this. It is also reasonable to assume that the very enlarged 'pseudo Panum's areas' first described by Bagolini in 1970,¹ can be explained by this area of inhibition or by abnormal confluence of nerve paths in the 'where system' from the squinting eye. In long-standing abnormal correspondence the dominance of the undeviated eye's 'where system' becomes more fixed, perhaps because long-standing inhibition eventually becomes intractable. Under these circumstances the dominance of the 'where system' of the straight eye is likely to remain even if the squint is straightened surgically or the deviation relieved by prisms.

Although these 3 adaptations may be considered separately, in most unilateral squint the total adaptation will consist of an interplay of all 3. In very many cases, of alternating squint, however, the amblyopia may not be marked, and this suggests that inhibition in the 'where system' can occur independently of lateral conduction (or abnormal confluence) in that 'what system'.

Pursuit anomalies

It is a well known clinical observation that in many squints the ability of the eye to follow a moving target is impaired. This can be seen when undertaking the motility test for noncomitancy, not by any restriction of the total motor field, nor by an increase in the angle of squint in 1 direction, but by a failure of the deviating eye to follow the target. It may be assumed that this could be explained in terms of abnormal confluence or by inhibition of the 'pursuit system' (w cells). It is difficult to offer further explanation on this, as insufficient attention seems to have been given to analysing the anomalies of pursuit in squint.

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Depth perception in strabismus

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SUMMARY The monocular and binocular depth thresholds of strabismic subjects have been measured with a modified Howard-Dolman apparatus. Seven out of the 14 strabismic subjects tested were found to have binocular thresholds significantly higher than their monocular ones. These strabismic subjects all had small angles of deviation less than 8 prism dioptres and high acuities in both eyes.

The question whether strabismic subjects are able to utilise the cue of binocular parallax to see the world stereoscopically is of importance to both the clinician and the physiologist. While several researchers have reported stereopsis in strabismic subjects,¹⁻⁸ no research project has specifically investigated this topic.

It is well known that many monocular cues exist to aid stereopsis. Thus a person who is stereoblind, that is, unable to use disparity information to appreciate depth, can often give a positive response in certain stereo tests.⁹ The ability of stereoblind observers to use monocular cues may even be better than normal owing to their greater reliance on this type of information.

The problem of being able to differentiate between monocular depth perception and stereopsis can be solved by measuring depth discrimination both monocularly and binocularly and taking any difference as a measure of stereopsis. None of the papers cited above have reported the use of this technique except that by Kani,⁸ whose work included one strabismic amblyope. Therefore the question whether strabismic subjects possess stereopsis is still open to debate.

In this paper we report on measures of the monocular and binocular depth threshold of a group of strabismic subjects using a series of stereo tests which include those commonly found in ophthalmic practices. The results are discussed in the light of detailed measurements of the binocular status of each subject.

Subjects and methods

The monocular and binocular depth thresholds of 9 normal and 14 strabismic subjects were measured

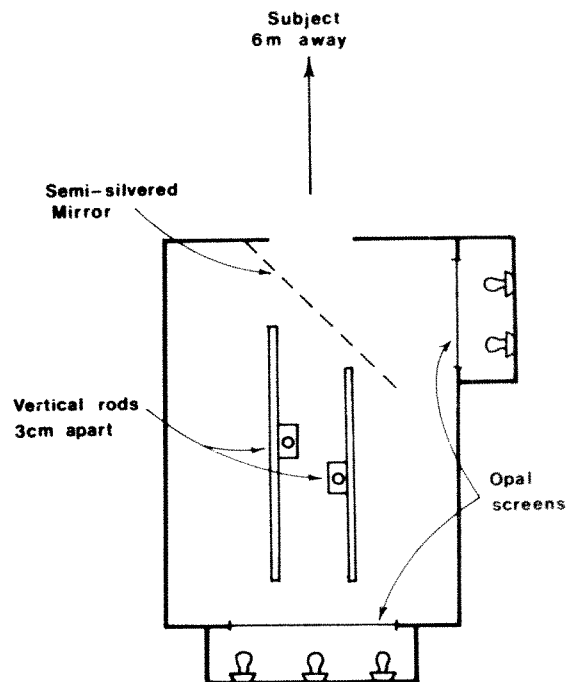


Fig. 1 A diagram of the modified Howard-Dolman apparatus as seen from above

with a modified Howard-Dolman apparatus.¹⁰ While the overall dimensions of the apparatus were the same as those in Howard's original instrument, certain modifications were included that allowed the exposure time and fixation to be controlled. A diagram of the apparatus is shown in Fig. 1. Situated between the front aperture and the $\frac{3}{8}$ in (9.5 mm) diameter rods was a semi-silvered mirror which reflected light from the side opal screen and transmitted light from the back opal screen. The lights

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Table 1 Result from the 7 strabismic subjects whose binocular depth thresholds were significantly lower than their monocular depth thresholds

Subj.	Age/Age of onset	R _x and V.A.	Angle of Squint (P.D.) s R _x c R _x	Test and density of ARC	Suppression Scotoma	Eccentric Fixation (P.D.)	Mon. thres. (cm)	Bin. thres. (cm)	Stereothreshold Titmus, Frisby, H-D (s of arc)
1	20.5 2	R +3.25 DS 6/5 L +2.75 DS 6/5	D 18 eso 3 eso Alt. N 20 eso 4 eso	ARC 1.6		None	11.95	3.00	40,15,10.6 3.98x
2	24.5 ?	R -5.50/-0.25 x 5 6/5 L -3.00/-1.25 x160 6/5	D 6 exo 6 exo Right N 6 exo 6 exo	ARC+ NRC 1.0		?	21.68	4.73	40,20,15.0 4.58x
3	20 5	R -1.75/-0.25 x 40 6/5 L -2.50/-0.50 x 80 6/5	D 3 eso 3 eso Left N 3 eso 3 eso	ARC 1.4		None	22.13	3.28	40,25,11.5 6.75x
4	19.5 6	R -3.50/-0.25 x 25 6/5 L -4.00/-0.26 x145 6/6	D 14 exo 4 exo Left N 30 exo 8 exo	ARC 1.8		1	18.88	5.87	40,75,21.0 3.22x
5	19.5 18	R +0.50/-0.50 x 15 6/6 L +0.75/-0.50 x165 6/6	D 8 exo 8 exo Intermittent N 10 exo10 exo	NRC		None	14.44	2.36	40,15,8.6 6.12x
6	19.5 4	R +3.50 DS 6/5 L +4.50 DS 6/6	D 16 eso 0 Left N 20 eso 3 eso	ARC 1.6		None	13.35	3.90	80,35,15.0 3.42x
7	15 2	R +5.25/-1.00 x180 6/9 L +4.75 DS 6/6	D 12 eso 5 eso Right N 16 eso 6 eso	ARC 1.4		None	21.2	2.75	40,20,10.0 7.71x

R_x = Prescription for spectacles. s R_x = Without prescription for spectacles. c R_x = With prescription for spectacles. V.A. = Visual acuity. ARC = Abnormal retinal correspondence. NRC = Normal retinal correspondence. x = Multiplication.

behind these 2 opal screens were controlled by a timing circuit which allowed only 1 set to be on at any given time. Before the subject triggered the timing circuit the lights behind the side opal screen would be on and the subject would see a fine black cross which was attached to the front of the side opal. This cross, which provided the subject with a fixation point, was positioned so as to be in line with the centre of the right rod. On triggering the timing circuit the lights behind the rear panel would come on and those behind the side opal panel go off for a period of 2 seconds, enabling the subject to see the two vertical black rods. The intensity of the background screens, as seen by the subject, was 1.80×10^2 cd/m².

Subjects were carefully aligned 6 metres away from the stationary rod, their heads being kept stationary with the aid of a chin and forehead rest. A forced-choice technique was used to establish the depth thresholds.¹¹

Three sets of readings were taken on each subject. The first of these was taken with the dominant or nondeviating eye only, the second set with both eyes, and the third set with the same eye as the first set. There was a half-hour break between each session. The experiment was conducted in this manner to establish whether there were any training or fatiguing effects.

The stereo acuity was also measured with the

Titmus and Frisby tests in the manner outlined in the instructions provided with each test.

In addition to measuring the depth thresholds the binocular status of the strabismic subjects was established with the following tests. Firstly, the objective angle of deviation was measured distance and near, with and without spectacle corrections, by a prism bar and cover test. The degree of eccentric fixation was measured by Haidinger's brushes in conjunction with a tangent screen. And the presence of abnormal retinal correspondence (ARC) or suppression was detected with a Bagolini striated lens in conjunction with a neutral density filter bar (in steps of 0.2 log units), as described by Mallett.¹²

All normal subjects had acuities of 6/6 or better in both eyes and wore their correcting spectacles (if any) throughout the duration of the experiment.

Results and discussion

The results from the strabismic subjects are given in Tables 1 and 2.

The stereo thresholds for the Titmus test were obtained from the data supplied with the test. The values for the Frisby test were obtained from the corrected tables published by Frisby.¹³ The monocular and binocular depth thresholds for each session on the Howard-Dolman apparatus were obtained both by calculation and by measurement

Table 2 Results from the 7 strabismic subjects whose monocular and binocular depth thresholds were essentially the same

Subj.	Age/Age of onset	R_x and V.A.	Angle of Squint (P.D.) $s R_x$ $c R_x$	Test and density of ARC	Suppression Scotoma	Eccentric Fixation (P.D.)	Mon. thres. (cm)	Bin. thres. (cm)	Stereothreshold Titmus, Frisby, H-D (s of arc)
8	21 4	R +1.50/-0.75 x165 6/9 L +2.25/-0.75 x 60 6/5	D 25 eso 12 eso Right N 25 eso 12 eso	ARC 0.6		None	12.2	10.45	800,-,- 1.17x
9	18 0	R -3.00/-0.50 x 15 6/5 L -2.50/-0.50 x 30 6/5	D 40 eso 35 eso Right N 35 eso 35 eso	ARC 0.4		1	16.08	14.18	-,-,- 1.13x
10	17 3	R +3.50/-0.50 x 30 6/9 L +2.00 DS 6/5	D 35 eso 25 eso Right N 35 eso 25 eso	Sup		2	13.35	13.80	-,-,- 0.98x
11	50 ?	R +5.75/-0.50 x 30 6/9 L +5.50/-1.00 x175 6/6	D 8 eso 8 eso Alt. N 12 eso 10 eso	ARC 1.4		None	9.65	12.00	800,-,- 0.80x
12	18 4	R +3.00/-0.50 x180 6/9 L +2.00/-0.50 x180 6/5	D 12 eso 5 eso Right N 12 eso 5 eso	ARC 0.8		None	14.63	13.58	200,150,- 1.08x
13	35 1	R +3.50/-0.25 x 90 6/5 L +4.00/-0.50 x 50 6/36	D 10 exo 12 exo Left N 6 exo 6 exo	Sup		?	-	-	-,-,-
14	55 0	R +5.50/-0.75 x 10 6/6 L +6.25 DS 6/18	D 8 exo 8 exo Left N 10 exo 10 exo	Sup		2	-	-	400,340,-

Abbreviations as in Table 1.

from an ogive. (The techniques used to calculate the stereo threshold by both calculation and measurement are fully described in Woodworth and Schlosberg.¹¹) In the majority of cases these 2 techniques yielded similar results. In the few cases when they did not the data from the ogive were used. The final monocular threshold was taken as an average of the values obtained from the 2 monocular sessions.

Seven of the 14 strabismic subjects who took part in this project showed a binocular depth threshold significantly better than their monocular thresholds with the Howard-Dolman apparatus. Their binocular thresholds ranged from 8.6 to 21 seconds of arc. The average binocular threshold for normal subjects with this apparatus was 5.8 seconds of arc (SD 2.2). Thus the strabismic subjects had in all cases thresholds above the normal.

A graph of the ratio of the monocular threshold to the binocular threshold versus the angle of deviation is given in Fig. 2. It can be seen from this figure that it is only those subjects with angles of deviation which fall in the microtropic range (1-5 degrees according to Lang¹⁴) who had fairly good stereo acuities. The habitual angles of deviation of these subjects did not exceed 6 prism dioptres of esotropia and 8 prism dioptres of exotropia.

All of the subjects with binocular thresholds significantly above their monocular acuities had no more than a 1-line difference between the visual acuities of the 2 eyes, the better eye having a mini-

mum acuity of 6/6. This parameter is not, however, a good indicator of stereo acuity in strabismic subjects, as several subjects with very poor stereo acuity also had high visual acuities in both eyes. It does seem, however, that strabismic subjects with low visual acuity in one or both eyes are unlikely to have a high stereo acuity.

It can also be seen from Fig. 2 that while all subjects with high stereo acuity had a microtropia

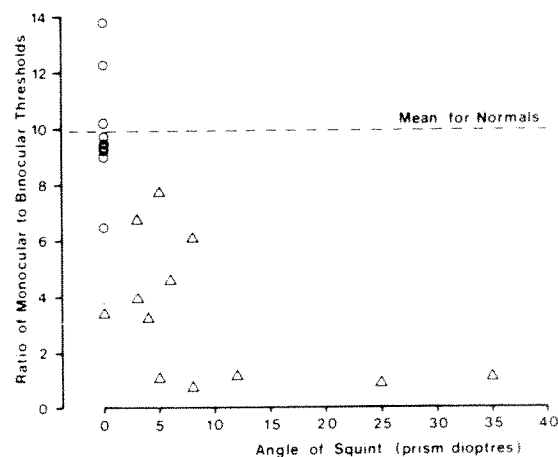


Fig. 2 The ratio of the monocular to binocular depth thresholds for the 9 normal subjects ($\circ$) and the 14 strabismic subjects ($\triangle$)

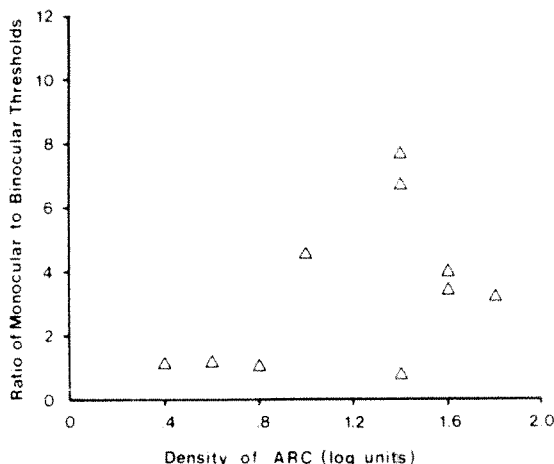


Fig. 3 The ratio of monocular to binocular depth threshold versus density of ARC in the strabismic subjects

there were 2 subjects with microtropia who did not have a high stereo acuity.

Five of the 7 subjects with high stereo acuities gave responses of harmonious abnormal retinal correspondence (ARC) whilst the sixth subject gave a mixed response of normal retinal correspondence (NRC) and ARC and the seventh subject showed NRC. The subject who showed NRC had only recently been diagnosed as strabismic.

A graph of the ratio of monocular to binocular depth threshold versus the density of ARC is given in Fig. 3. There is a correlation coefficient of 0.48 between these 2 measures, a finding which gives support to Mallett,⁷ who stated that where the angle of deviation is small the ARC is generally well established and the binocularity of a high order. Of the 7 remaining subjects who had either gross stereopsis or no stereopsis at all 4 had only lightly ingrained ARC while the remaining 3 showed obligatory suppression.

The average monocular depth threshold for the 14 strabismic subjects was found to be 15.8 cm (SE 1.1), while that for the normals was 12.9 (SE 0.8). These values are not significantly different at the 10% level. Dividing the strabismic subjects into those with stereopsis and those without yields values of 17.7 cm (SE 1.6) and 13.2 cm (SE 1.1) respectively. The average monocular depth thresholds were also measured in 2 monocular subjects and found to be 23.3 cm and 15.3 cm. There does not, therefore, seem to be any evidence within this experiment to support the idea that those subjects with deficient stereopsis have developed their abilities to use monocular cues beyond that of normal persons.

Three different tests were used to measure the stereo acuity in the strabismic subjects, namely, the Howard-Dolman test, the Titmus test, and the Frisby test. The stereo acuities recorded with the Howard-Dolman apparatus were higher than those recorded with the Titmus and Frisby tests. This difference could be due either to the difference in the nature of the tests or to the difference in the testing distances.

Both the Titmus and Frisby tests correlated fairly well with the Howard-Dolman test in that all of the strabismic subjects with stereopsis obtained fairly good stereo acuity measures with both the Titmus and Frisby tests. Although the Titmus test could distinguish strabismic subjects with stereopsis from those without, it was unable to distinguish strabismic subjects with stereopsis from normal persons, as the limiting threshold of this test is 40 seconds of arc. The highest disparity settings of the Titmus test (400+800 seconds) seem to be of little value, as most people can distinguish which is the eccentric spot with one eye closed and the practitioner has no evidence as to whether the subject is responding to this cue or to the correct one.⁹

Conclusions

Seven out of 14 strabismic subjects were found to have stereo acuities significantly better than their monocular depth thresholds when tested with a modified Howard-Dolman apparatus. None of the strabismic subjects had stereo acuities as high as the average for normal persons measured with the same instrument. The strabismic subjects with stereopsis all had angles of deviation below 8 prism dioptres and high monocular acuities. The results from the Titmus and Frisby stereotests correlated fairly well with the results from the Howard-Dolman test. The monocular depth threshold of strabismic subjects was found to be no different from that of normal persons.

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Torsional fusional vergences and assessment of cyclodeviation by synoptophore method

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SUMMARY Two special slides, one in front of one eye and one in front of the other eye, were placed in the housings of a synoptophore. The slides were originally designed for the diagnosis and measurement of cyclodeviation, but they were utilised in this study for the measurement of torsional fusional vergence. This was measured by rotating one of the housings of the synoptophore and noting the point of appearance of cyclodiplopia, which was taken as the end point. For measuring vertical torsional fusional vergence the subject was required to fuse the vertical line of the slide with the circle and the vertical line of the slide with the cross, and for measuring horizontal torsional fusional vergence he was required to fuse the horizontal line of the slide with the circle and the horizontal line of the slide with the cross. Incyclovergence was found to be greater than exyclovergence in all the 3 positions of gaze (straight, up, down) studied. The mean amplitude of torsional fusional vergence was lowest in the primary position. Torsional fusional vergence was much less with horizontal lines than with vertical lines in all positions of gaze. The use of the horizontal line of the slide with the cross would be more advantageous for the diagnosis and measurement of cyclodeviation by the synoptophore method, as the amplitude of cyclofusion is minimal in the horizontal meridian.

After the publication of the paper on diagnosis and measurement of cyclodeviation by the synoptophore method with the help of 2 special slides¹ some ophthalmologists working with these slides experienced difficulties in clinical practice as the upright lines could be fused by some patients. This eliminated some of the torsional error, making maximum cyclodeviation difficult to assess in these patients.

It is granted that torsional fusional vergence may mask some cyclodeviation during its measurement with these slides unless care is taken to reduce it to minimum. One way of doing it is to ask the patient not to make any conscious effort to bring about fusion of the lines but to report as soon as cyclodiplopia is experienced. Moreover, it is accepted that that part of cyclodeviation which can be controlled by normal torsional fusional reserve with ease and comfort needs no treatment and therefore can be ignored in clinical practice. Nevertheless a study was undertaken to find out the amplitude of torsional fusion in normal subjects with vertical and horizontal lines, and that forms the basis of this report.

Subjects and methods

Forty normal subjects from 18 to 25 years of age with normal binocular functions and without any refractive error were taken for this study.

The subject was placed in front of a synoptophore. Slide 1, a black circle with its circumference marked in degrees and with 2 lines, one vertical and the other horizontal, passing through its centre (Fig. 1), was placed upright before one eye and slide 2, a black cross (Fig. 2), was likewise placed before the other eye. Slides 1 and 2 have been described in detail previously.¹ The arms of the synoptophore were so set that the small black dot in the intersection of the cross in slide 2 coincided exactly with the small circle in the centre of the large circle in slide 1, and the vertical and the horizontal lines of the cross in slide 2 coincided exactly with the vertical and the horizontal lines respectively of slide 1.

For measuring torsional fusion a tilt of the vertical line of the cross in slide 2 was caused by wheel-rotating the slide by means of the torsional deviation screw of the synoptophore. The tilt was gradually increased till a point was reached when the person could no longer maintain fusion of the 2

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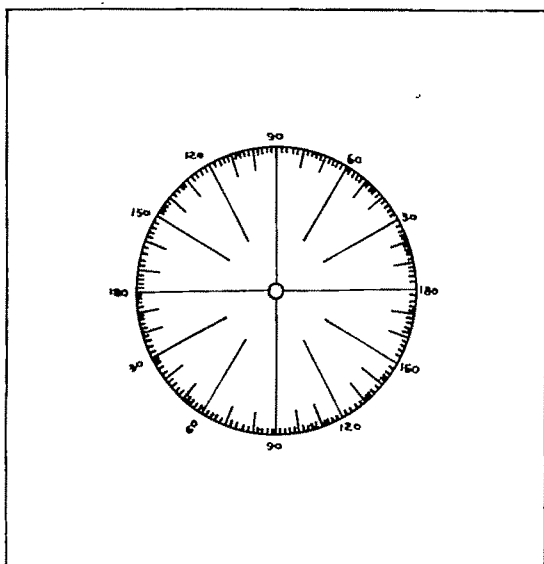


Fig. 1 Slide 1 showing the black circle with the vertical and the horizontal lines

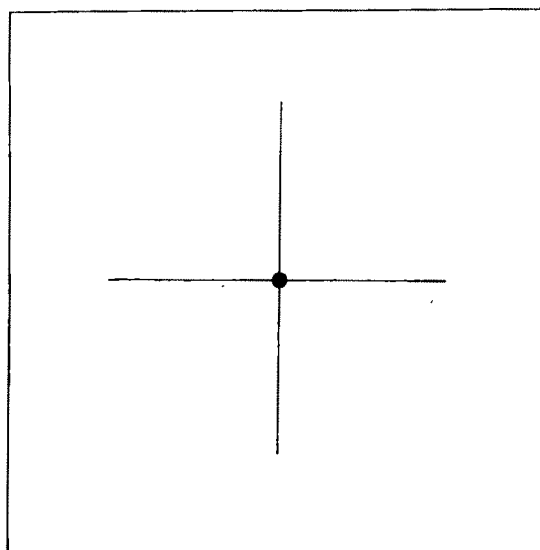


Fig. 2 Slide 2 showing the black cross for use in conjunction with slide 1

vertical lines and reported the appearance of cyclodiplopia. The person was encouraged all the time to maintain fusion of the 2 vertical lines through maximum effort. The amount of tilt of the vertical line of the cross in slide 2 causing cyclodiplopia was read in degrees from a scale provided in the synoptophore. Then a tilt of the vertical line of the cross in slide 2 in the opposite direction was caused by wheel-rotating the slide in the opposite direction, and the whole procedure was repeated with the point when cyclodiplopia appeared taken as the end point.

In a similar way the torsional fusional vergence was measured with the horizontal line of the cross in slide 2 and the horizontal line in slide 1.

Results

A set of 12 observations were made on each of 40 subjects covering every combination of 3 positions (primary, looking up, and looking down), 2 axes (vertical and horizontal), and 2 vergences (incyclovergence and exyclovergence). The observed values are summarised in Table 1, which gives

Table 1 Torsional vergences in different positions of gaze in vertical and horizontal meridians

	With vertical lines			With horizontal lines		
	Min.	Max.	Mean $\pm$ SD	Min.	Max.	Mean $\pm$ SD
Primary position:						
Incyclovergence	1	15	5.25 $\pm$ 2.73	1	6	3.40 $\pm$ 1.28
Exyclovergence	1	10	4.15 $\pm$ 1.86	1	6	2.58 $\pm$ 1.26
Amplitude	4	20	9.40 $\pm$ 3.93	2	10	5.98 $\pm$ 2.25
Looking up by 25°:						
Incyclovergence	2	14	5.88 $\pm$ 3.06	1	11	3.83 $\pm$ 1.97
Exyclovergence	1	13	4.93 $\pm$ 3.24	1	11	2.75 $\pm$ 1.75
Amplitude	4	26	10.80 $\pm$ 5.91	2	22	6.58 $\pm$ 3.55
Looking down by 25°:						
Incyclovergence	1	11	5.00 $\pm$ 2.57	1	8	3.60 $\pm$ 1.57
Exyclovergence	1	13	4.83 $\pm$ 2.65	1	5	3.18 $\pm$ 1.26
Amplitude	4	23	9.83 $\pm$ 4.52	2	13	6.78 $\pm$ 2.54

Table 2 *Torsional vergences: analysis of variance*

Source of variation	Degrees of freedom	Sum of squares	Mean SS	F	P
Between positions	2	20.33	10.16	3.56	<0.05
Between axes	1	381.63	381.63	133.91	<0.001
Between vergences	1	69.00	69.00	24.21	<0.001
Between subjects	39	972.92	24.95	8.75	<0.001
Position/axes interaction	2	7.21	3.60	1.26	>0.05
Position/vergences interaction	2	12.67	6.34	2.22	>0.05
Axes/vergences interaction	1	0.04	0.04	0.01	>0.05
Position/axes/vergences interaction	2	1.49	0.74	0.26	>0.05
Residual	429	1220.64	2.85	—	—
Total	479	2685.93	—	—	—

minimum, maximum, and mean values for each combination as well as similar data for amplitude of vergences.

Further statistical analyses have been carried out by regarding the experiment as one with a factorial design with 3 levels of positions, 2 levels of axes, and 2 vergences. The analysis of variance is set forth in Table 2.

It can be seen that differences in the 'levels' of all three factors are statistically significant. Values for the primary position are the lowest of the 3 positions studied and are significantly lower than for looking up and looking down positions. Values in the horizontal axes are significantly lower than in the vertical axes. Exyclovergence values are significantly lower than incyclovergence values. None of the interactions is statistically significant.

Taking into account all these findings we can say that the lowest overall value out of the various combinations of positions, axes, and vergences can be had from the primary position, horizontal axes, and exyclovergence. This can also be verified from the actual observations made in this study (Table 1), from which one finds that of all the

combinations the lowest mean (2.58) was obtained from this particular combination.

A similar analysis was carried out for the amplitude of the vergences for each combination of position and axis. The results are set out in Table 3.

The differences between the 3 positions fail to attain statistical significance, but there is a highly significant difference between the horizontal and vertical axes. Values for the former are thus found to be lower than for the latter, a difference which was earlier noted in respect of the original values for exyclovergence and incyclovergence in Table 2.

Discussion

Reported data on torsional fusional vergences are scanty. Though a few studies are available, they are not comprehensive. There is no study in which the torsional fusional vergence has been measured in both vertical and horizontal meridians and in different positions of gaze.

Even in the published data there is some disagreement as to whether incyclovergence³ or exyclovergence^{3,4} is greater. Bullock³ found incyclover-

Table 3 *Amplitude of torsional vergences: analysis of variance*

Source of variation	Degrees of freedom	Sum of squares	Mean SS	F	P
Between positions	2	40.68	20.34	1.3	>0.05
Between axes	1	763.27	763.27	49.1	<0.001
Position/axes interaction	1	14.40	14.40	1.08	>0.05
Residual	235	3653.50	15.55	—	—
Total	239	4471.85	—	—	—

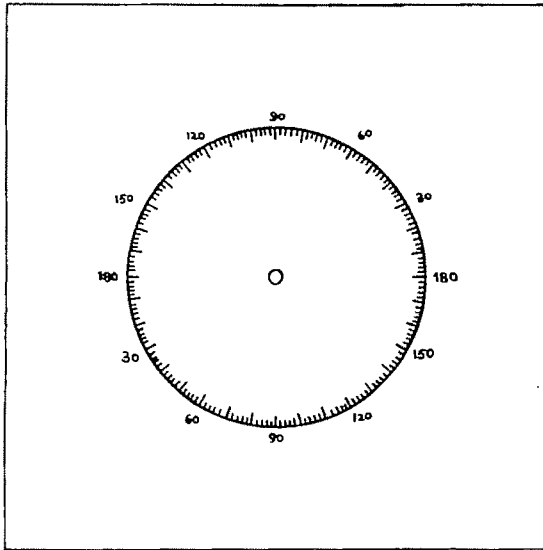


Fig. 3 Modified slide 1 showing that none of the markings on the circumference of the circle extends towards the centre in the form of long lines. This modified slide is now recommended for use in conjunction with slide 2 for the diagnosis and measurement of cyclodeviation

gence to be 6° to 10° and exocyclovergence to be 4° to 8° . Parks⁴ stated that a normal person had an incyclovergence of 6° to 10° and an exocyclovergence of 8° to 12° . The present study shows that the mean incyclovergence is greater than the mean exocyclovergence in all the 3 positions of gaze studied. However, the range of incyclovergence and exocyclovergence varied with the positions of gaze and also with the direction of the lines to be fused. In the primary position the range of incyclovergence was between 1° to 15° with the vertical lines and between 1° to 6° with horizontal lines; the range of exocyclovergence was between 1° to 10° with the vertical

lines and between 1° and 6° with horizontal lines.

It has been stated²⁻⁵ that the amplitude of torsional fusional vergences are between 4° and 12° . However, our values in the primary position are between 4° and 20° with vertical lines and between 2° and 10° with horizontal lines. Our study also shows that the amplitude of torsional fusional vergences are much less with horizontally placed lines than with lines vertically placed in all the 3 positions of gaze studied. This finding is interesting and has an important clinical implication in that, while measuring cyclodeviation by the methods previously described¹ the horizontal line of the cross in slide 2 can be used with greater advantage for bringing out maximum cyclodeviation, as less of it can be masked by torsional fusional vergences. However, it would be still better to modify slide 1 for the purpose of diagnosis and measurement of cyclodeviation so that the markings on the circumference of the circle do not extend towards the centre in the form of long lines. Such extension of the markings has not been found to be of any particular advantage during the testing for cyclodeviation. On the other hand this modification will reduce the impulse for torsional fusion further during the testing for cyclodeviation by our method. The modified slide 1 which is now being used by us for the diagnosis and measurement of cyclodeviation by synoptophore method is shown in Fig. 3.

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Treatment of bilateral superior oblique tendon sheath syndrome complicating rheumatoid arthritis

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SUMMARY A patient with well established seropositive rheumatoid disease developed bilateral superior oblique tendon sheath syndromes. Treatment with local injections of corticosteroids is described.

Case report

A 63-year-old retired mining engineer with rheumatoid arthritis presented in November 1976 with intermittent diplopia on upward gaze. His diplopia became increasingly troublesome, particularly on waking, and he was admitted under the care of the rheumatologists for investigation in February 1977.

He had a 6-year history of seropositive erosive rheumatoid arthritis with numerous extra-articular features, including weight loss, subcutaneous nodules, Raynaud's phenomenon, mild bilateral carpal tunnel syndrome, nail fold vasculitis, hepatosplenomegaly and pericarditis.

INVESTIGATIONS

The differential agglutination test for rheumatoid factor was positive 1/1024; antinuclear factor negative; erythrocyte sedimentation rate 42 mm/1st hour; and full blood count normal, including differential white cell count. Thyroid function tests were normal and thyroid antibodies negative; tests for antismooth muscle and antimitochondrial antibodies were negative. The immunoglobulin profile was normal; serum alkaline phosphatase slightly elevated, but other liver function tests were normal. Technetium scan of liver and spleen showed a smooth uptake; liver biopsy was normal and sections stained for amyloid were negative. Lymph node biopsy showed reactive hyperplasia but no infiltrate.

OCULAR FINDINGS

In September 1977, as the diplopia was still present,

he was referred to the ophthalmology department.

On examination his corrected visual acuities were 6/9 in each eye. Cover test showed a slight alternating hyperphoria. There was bilateral limitation of elevation in adduction and downshoot of each adducted eye on lateral versions. No clicking sensation was noted. A Hess chart confirmed that he had bilateral superior oblique tendon sheath syndromes (Fig. 1).

PROGRESS

It was decided to treat his rheumatoid disease with weekly injections of intramuscular gold in the hope of controlling his general condition and his diplopia. Unfortunately he developed such violent reactions to the injections in the form of rigors and joint pains that they had to be stopped after 6 weeks. Penicillamine was then cautiously introduced, but he soon developed diarrhoea and a rash, so therapy was discontinued. His rheumatoid disease was therefore controlled with indomethacin and aspirin.

As his diplopia persisted, in March 1978 he was given an orbital injection of 1 ml (40 mg) of methylprednisolone acetate (Depomedrone) over the superomedial aspect of the left globe. Some lessening of his diplopia and improvement in his Hess chart were noted, and therefore a week later a similar orbital injection was given on the right side. A month later the patient was symptomatically very much improved, experiencing diplopia only on extreme upward gaze. A Hess chart recorded on this occasion is shown in Fig. 2.

Six months later his diplopia began to return and by March 1979 was no longer tolerable. Ocular examination and Hess chart (Fig. 3) showed a recurrence of his bilateral superior oblique tendon sheath syndrome. Orbital injections of 1 ml of

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methylprednisolone acetate were given superomedially over each globe. Four weeks later he had improved greatly subjectively and objectively (Fig. 4) and remains asymptomatic 3 months after these injections.

Discussion

Harold Brown¹ described the superior oblique tendon sheath syndrome which has since been called Brown's syndrome. The syndrome was

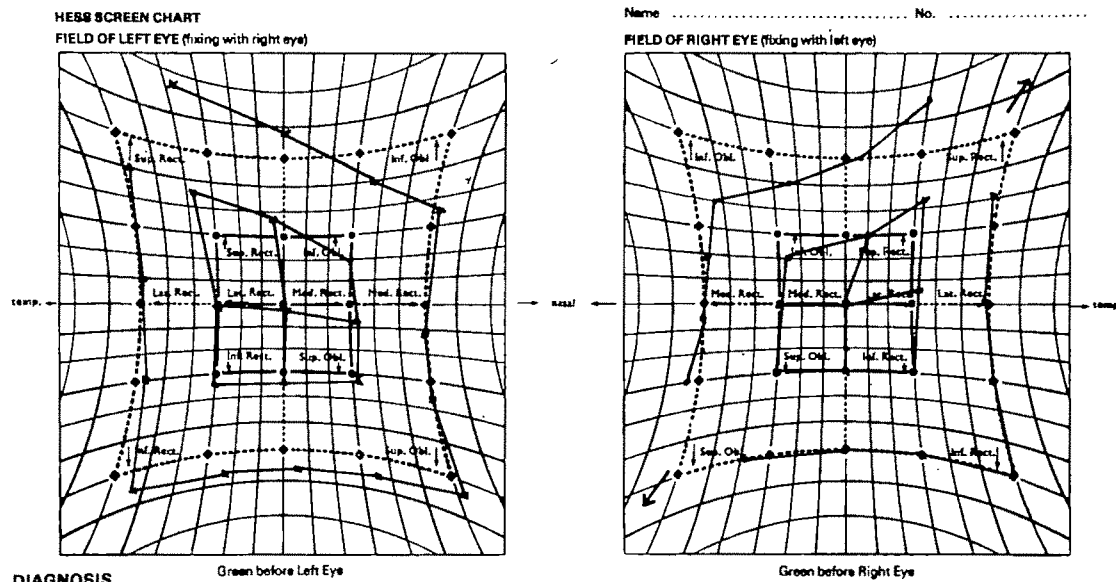


Fig. 1 Hess chart in September 1977.

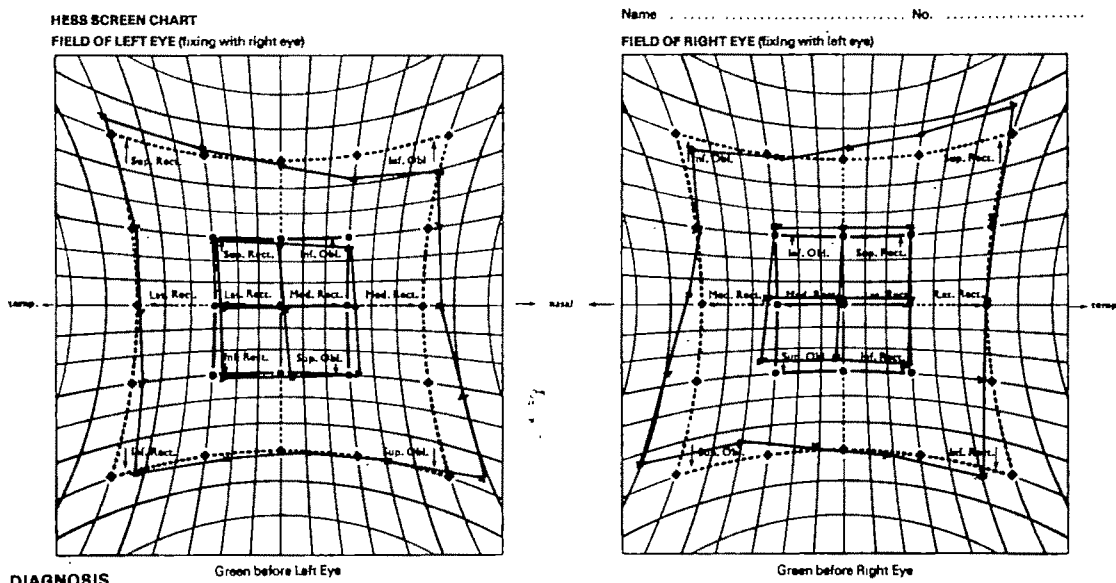


Fig. 2 Hess chart in April 1978.

initially thought to be the result of a congenital paralysis or delay in function of the inferior oblique muscle. This was postulated to lead to a thickening and shortening of the anterior sheath of the superior oblique, which is the check ligament of the inferior

oblique muscle. The various theories of the aetiology of the syndrome are well reviewed by Mein² and Sandford-Smith.³

Brown⁴ expanded the description of the syndrome, separating it into true and simulated sheath syn-

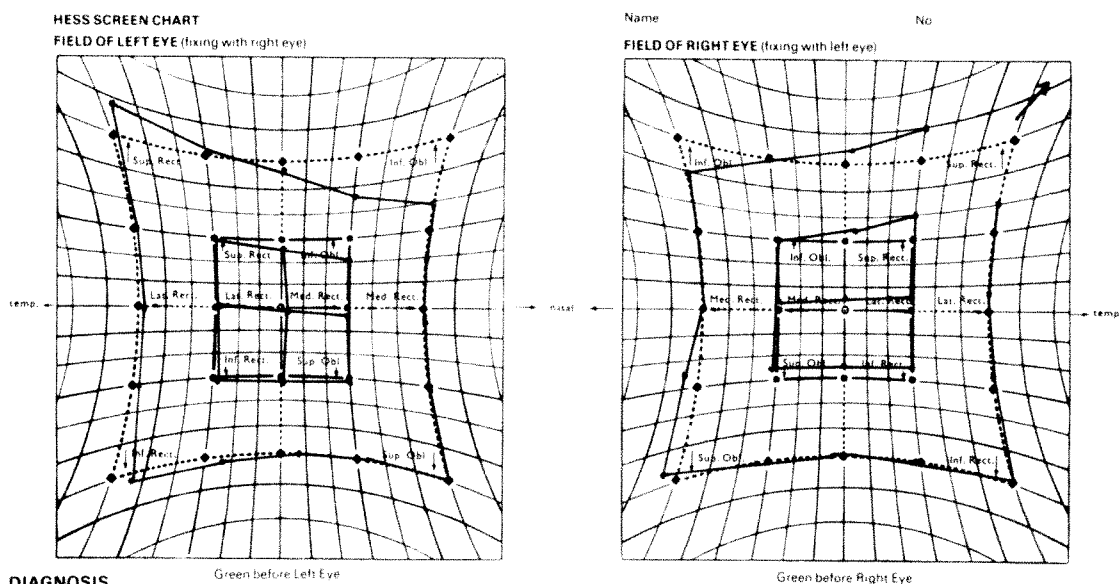


Fig. 3 Hess chart in March 1979.

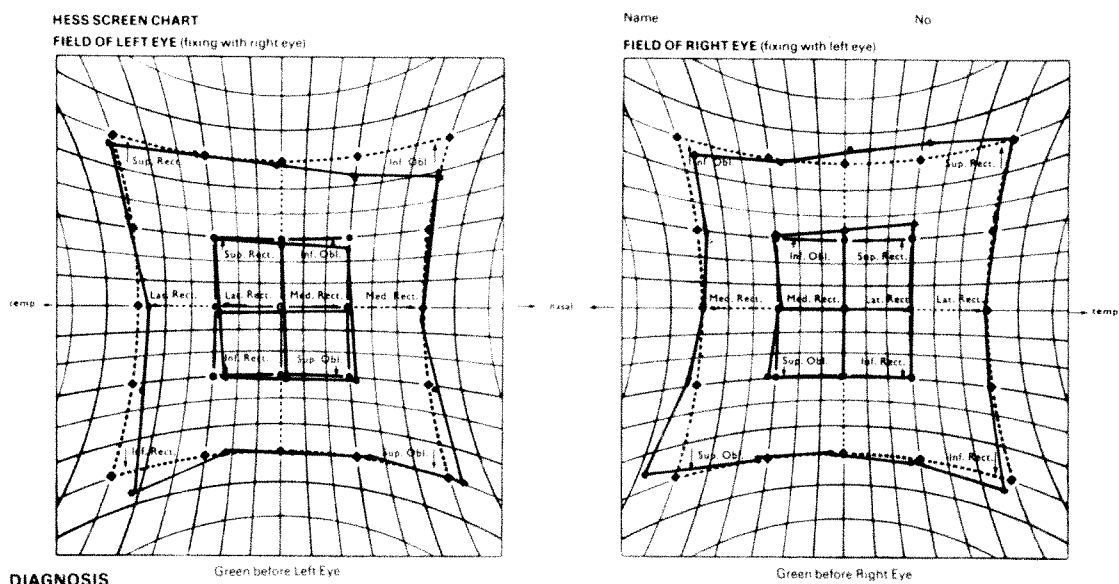


Fig. 4 Hess chart in April 1979

dromes. The true sheath syndrome is always congenital and never disappears spontaneously. The simulated syndrome, however, may be congenital or acquired, may be intermittent and sometimes even undergo spontaneous recovery. The acquired simulated sheath syndrome has been described in association with ethmoiditis, orbital floor fractures, tucking of the superior oblique tendon, and rheumatoid arthritis.

Various surgical procedures designed to ameliorate the condition by weakening the superior oblique tendon have been reported.⁸ We describe the treatment of bilateral superior oblique tendon sheath syndromes with local injection of steroids in a patient with rheumatoid arthritis. As the patient improved both subjectively and objectively after

each steroid injection, it seems unlikely that this was due to spontaneous recovery.

We thank Mr M V Graham and Dr George Nuki for permission to publish this case.

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The oculocardiac reflex as a surgical aid in identifying a slipped or 'lost' extraocular muscle

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SUMMARY The oculocardiac reflex during strabismus surgery has generally been regarded as a hazard capable of causing death. Six cases are presented which show a beneficial use of the oculocardiac reflex. Isolation of a previously slipped or 'lost' extraocular muscle can be difficult. In this series identification of the tissue as muscle was substantiated by observing a positive oculocardiac reflex when traction was placed on the suspected tissue. Each of the 6 dislodged extraocular muscles was the medial rectus muscle. Three of the muscles had been resected and 3 either recessed or tenotomised. In one patient, despite 6 previous strabismus operations, including 2 strabotomies on a muscle that slipped, and in another patient, who had a lapse of 6 years since the last strabotomy, when the slipped muscle was isolated, the oculocardiac reflex could still be elicited. To avoid abolishing the oculocardiac reflex during surgery the anaesthetist should be instructed to avoid the use of an intravenous parasympatholytic agent, such as atropine, at the time of induction and during the operation.

Ophthalmologists and anaesthetists have regarded the oculocardiac reflex as an intraoperative hazard. This awareness is justified, since the resultant dysrhythmias have caused morbidity and even death. This reflex is usually caused by traction on the extraocular muscles, which, through the ophthalmic branch of the trigeminal nerve, stimulates the vagal centre. The vagus nerve then may cause a bradycardia or other dysrhythmia. A definition of a positive oculocardiac reflex has not been universally accepted. Some authors have used a bradycardia exceeding 10% of the premonitory heartbeat or any dysrhythmia as the criteria for a positive reflex.^{1,2} Because of our concern about this reflex we previously reviewed the topic and characterised the incidence of the reflex in regard to individual extraocular muscles, sex of patients, laterality, reproducibility, and type of general anaesthesia.³

The present report presents a beneficial use of the oculocardiac reflex. In the course of the previous study, and subsequently, we utilised the reproducibly positive oculocardiac reflex to identify a slipped or 'lost' muscle in a group of patients who had previous strabismus surgery.

The same anaesthetic routine and method of study was used in the group of patients with a slipped or 'lost' muscle as was used in the 243 patients in our previous report. Pethidine (Demerol)

and atropine or scopolamine were given 1.5 to 2 hours before surgery. No atropine or scopolamine was given thereafter. Local anaesthesia was not used. Halothane, given endotracheally, was the general anaesthetic agent. When the patient was on the operating table, 4 electrocardiogram leads were attached to his extremities and a baseline recording of the cardiac rate and rhythm was made. If the rate and rhythm was normal, surgery began. The electrocardiogram ran continuously during the operation. After isolation of the tissue suspected to be the slipped or 'lost' muscle, traction was applied to it with a muscle hook or forceps. A positive oculocardiac reflex response was designated as any dysrhythmia or a bradycardia of 10% or greater, as compared to the cardiac rate on the electrocardiogram tracing just before traction was applied.

We describe herein the clinical history and operative findings in 6 patients.

Case reports

CASE 1

An 11-year-old boy came to the Jules Stein Eye Institute with a history of congenital esotropia. He had undergone 6 previous operations on the extraocular muscles. At 30 months of age he had a recession of both medial rectus muscles, followed 1 year later by tenotomies of both inferior oblique muscles. Seven months later he had a myectomy of the right inferior oblique muscle and a resection of the left

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lateral rectus muscle. At 6 years of age a recession of the right superior rectus muscle and a resection of the right lateral rectus muscle was performed. At 9 years of age, to correct the residual esotropia, the surgeon re-recessed the left medial rectus muscle. Postoperatively the left eye was exotropic 20 prism dioptres and did not adduct past the midline. His sixth operation, performed 1 year later, consisted of lysis of adhesions around the supposed left medial rectus tendon and advancement of the supposed tendon. The left exotropia persisted postoperatively, and the patient was referred for consultation to one of the authors (L.A.).

Examination of the patient's eyes showed a left exotropia of 20 prism dioptres at distance and 30 prism dioptres at near, a left hypertropia of 6 prism dioptres, and an inability to adduct the left eye past the midline.

At operation forced ductions under general anaesthesia showed a moderate resistance to adduction of the left eye. At the original insertion site of the left medial rectus a band of tissue was found and a biopsy was done. The biopsy specimen later revealed fibrous connective tissue with inflammatory changes but no striated muscle fibres. Careful repeated passage of a muscle hook into the nasal area of the posterior globe yielded a small band of pink tissue. Before disinserting the band of pink tissue, to be sure the tissue contained extraocular muscle, traction was applied while monitoring the heart rate on an electrocardiogram. This manoeuvre caused the heart rate to decrease from 96 to 65 beats per minute. The band was disinserted and attached to the sclera 4 mm behind the limbus. In addition the left lateral rectus muscle was recessed 7 mm, and adhesions around it were lysed. The left inferior oblique muscle, found attached to the original insertion site, was recessed 10 mm. A stay suture was used to anchor the left eye in an adducted position for 6 days.

Postoperatively the left eye was mildly esotropic, but adduction of the left eye was regained.

CASE 2

A 26-year-old woman had a congenital left sixth nerve palsy. At 18 years of age her previous ophthalmologist performed an operation on the left eye, which consisted of transpositions of portions of the superior and inferior rectus muscles to the area of the lateral rectus muscle and a 'controlled tenotomy' of the medial rectus muscle. Postoperatively she developed an exotropia, mild dilatation of the left pupil, and head turn.

At 24 years of age she came to us with a visual acuity correctable to 6/6 (20/20) in the right eye and 6/7.5 (20/25) in the left eye. She had a head turn

to the right and a left exotropia of 32 prism dioptres at distance and 38 prism dioptres at near. Movement of the left eye was slight in abduction, and no movement occurred beyond the midline in adduction. Interestingly, the left palpebral fissure narrowed in adduction and widened in abduction.

At surgery, done under general anaesthesia, forced duction manoeuvres indicated resistance of the left eye to adduction and to elevation. The area of the left lateral rectus muscle was cleared of adhesions. During an attempt to isolate the left medial rectus muscle the hook encountered a fibrous-appearing band located only 2 mm behind the original insertion site. Decrease in the heart beat from 80 to 65 beats per minute was caused by traction on this band. The left lateral rectus muscle was recessed 8 mm and the newly identified left medial rectus muscle resected 7 mm. Traction sutures kept the eye in adduction postoperatively.

In the 2½ years since the operation the patient has had no head turn nor any heterotropia in the primary position. Both abduction and adduction of the left eye have improved but remain limited.

CASE 3

This girl was 5 years old when she was first seen at the Jules Stein Eye Institute. At 3 years of age she had a recession of the right medial rectus and a tuck of the right lateral rectus muscle for esotropia. She developed an incomitant exotropia—40 prism dioptres in left gaze, 18 prism dioptres in primary position, and no deviation on right gaze. Six months later surgical exploration disclosed tissue, thought to be the right medial rectus, located 15 mm from the limbus. This tissue was advanced to the original medial rectus insertion site. The eye alignment did not change after the second operation.

Our examination showed 6/9 (20/30) visual acuity in each eye, 5 prism dioptres exophoria with left head turn, but with the head held straight, an exotropia of 25 prism dioptres at distance and 30 prism dioptres at near. The right eye was capable of only slight adduction past the midline.

At operation forced duction tests under general anaesthesia were negative. The sclera at the original insertion site of the right medial rectus was thin, with dark uvea shining through. Exploration revealed a band of tissue located about 13 mm from the limbus. Traction on this band decreased the heart rate from 110 to 70 beats per minute. The band, which appeared mostly fibrotic, was attached 4 mm from the limbus below the area of thin sclera. The right lateral rectus was recessed 6 mm.

After the operation, the patient had no head turn, a small-angle esotropia, and good adduction of the right eye.

CASE 4

A 5-year-old girl had intermittent exotropia since 9 months of age. She had a recession of the right lateral rectus and a resection of the right medial rectus muscles. On discharge from the hospital the morning after surgery the eyes were straight, but when the patient was seen on the sixth day after surgery she had a right exotropia of 30 prism dioptres with markedly decreased adduction of the right eye. The palpebral fissure widened in attempted adduction.

Eight days after the first operation she was operated upon at the Jules Stein Eye Institute. Forced duction tests under general anaesthesia were negative. At operation 1 double-armed and 1 single-armed suture, used to attach the right medial rectus muscle to the sclera, were still in position with the knots apparent. Only some strands of muscle were attached at the superior end of the insertion site. In exploring for the remainder of the muscle traction applied to the fibres which were thought to be muscle caused the heart rate to decrease from 100 to 85 beats per minute. These fibres were then attached to the original insertion site.

Three months after surgery the patient had an intermittent exotropia of 16 prism dioptres at distance and 22 prism dioptres at near with good adduction of the right eye.

CASE 5

This patient developed a large-angle exotropia in infancy. At 4 years of age her left lateral rectus muscle was recessed, and her left medial rectus muscle was resected. On the first postoperative day a small amount of esotropia was present. The left eye demonstrated normal ductions. Two days after surgery (and 1 day after discharge), while the child was thrashing and jumping about at home during a temper tantrum, her father noted a sudden 'turning out and no movement' of the left eye. On examination she had a left exotropia of 50 prism dioptres, inability to adduct the left eye past the midline, and widening of the palpebral fissure on attempted adduction.

Five days after her first operation she was returned to the operating room. Forced duction manoeuvres under general anaesthesia demonstrated a mild resistance to adduction of the left eye. Dissection at the original insertion site of the left medial rectus revealed that the double-armed suture was in place with a secure knot, but there was no tissue within the suture; only a bare scleral bed was visible. A muscle-like substance was found within Tenon's capsule. Traction on this tissue mass caused the heartbeat to decrease from 105 to 80 beats per minute. The tissue was advanced to the original

insertion site, and reattached. Two stay sutures were used to keep the eye adducted during the immediate postoperative period.

The resulting eye alignment was slight left exotropia with a mild decrease in the ability of the left eye to adduct.

CASE 6

This girl was 6 years of age when the diagnosis was made of a left exotropia associated with a double elevator palsy of the left eye. Surgery performed on the left eye consisted of upward transposition and recession of the lateral rectus muscle and upward transposition and resection of the medial rectus muscle.

The postoperative course was uneventful until the fourth day, when the father noted the sudden onset of the 'left eye going out'. Trauma was denied. On examination the patient had a large left exotropia with no adduction of the left eye past the midline.

Surgery was performed 7 days after the initial operation. Under general anaesthesia the forced duction test was negative. In the area of the insertion of the left medial rectus muscle the suture and knot were found properly in place in the sclera. However, no muscle was held within the suture. Slightly behind the equator a structure which appeared to be muscle was found. Traction on the structure produced a decrease in heart rate from 104 to 88 beats per minute. The muscle was advanced and sutured to the sclera in the previously intended site.

After operation most of the action of the left medial rectus muscle returned.

Discussion

Diagnosis of a slipped or 'lost' extraocular muscle shortly after strabismus surgery is suspected when limitation of globe movement in the field of action of the dislodged muscle is associated with a marked overcorrection or undercorrection in the primary position, or a sudden large shift in ocular alignment from that noted immediately after surgery. Voluntary movement of the globe beyond the midline is usually minimal. On attempted movement of the eye in the field of action of the dislodged muscle the eye protrudes and the palpebral fissure widens, because the antagonist muscle relaxes while the disengaged agonist has no retraction effect on the globe.

We want to emphasise another diagnostic clinical sign derived from our series of dislodged medial rectus muscles, namely, the amount of exotropia at near exceeds the amount of exotropia at distance. In the case of a dislodged lateral rectus muscle one

could expect the exotropia to be greater at distance than at near.

During the first weeks after a muscle is lost or has slipped the forced duction test is usually negative. However, after a few months the antagonist muscle may become tight, develop a contracture, and cause limited forced traction in the field of action of the disinserted muscle. At this stage enophthalmos may occur on gaze in the direction of reduced motility because the tight antagonist does not fully relax.

Saccadic velocity measurements in the early postoperative period reveal a reduced saccadic velocity of the posteriorly slipped muscle. A difference between agonist and antagonist saccadic velocity of 20% or greater strongly suggests a diagnosis of a slipped rectus muscle.⁴

The active force generation test described by Scott⁶ may disclose reduced or absent contracting power of the disengaged muscle. Scott⁶ also devised an electronic stimulator to identify a dislodged rectus muscle at the time of surgery.

Surgery for a suspected slipped or 'lost' rectus muscle is easier if performed soon after the muscle is dislodged, because the suture may still be seen attached to the muscle, and the muscle still has its reddish colour. Identification of the muscle may be more difficult, however, if a few weeks or months elapsed after the muscle disengaged. The area to be explored often has adhesions and extraneous tissue. As the surgeon seeks the muscle in question, he may have to lyse adhesions and judge if the tissue uncovered is or is not extraocular muscle. The muscle, especially the medial rectus, may have retracted into Tenon's capsule, and exploration along Tenon's capsule may reveal the muscle. Certain muscles have some form of weak attachment to other extraocular muscles that can aid the surgeon's exploration. For example, the lateral and inferior rectus muscles may be found by following the course of the inferior oblique muscle. Similarly, the superior rectus muscle may be found by following the course of the superior oblique tendon.⁷ Because the medial rectus muscle lacks even a loose attachment to another muscle, it is the muscle that usually is the most difficult to retrieve. In our 6 cases the medial rectus was the muscle that became dislodged.

A general belief is that a resected muscle tends to slip more than a recessed muscle, because of the greater tension placed on it. This may be true, but only half of the lost medial rectus muscles in our series had been resected, and the other 3 were either recessed or tenotomised.

Once the alleged extraocular muscle is found, it is not always easy to be sure it is truly muscle. Depending on the interval from the time the muscle

was dislodged, fibrosis may have occurred. With fibrosis the structure loses the reddish striations characteristic of muscle, and it appears as a homogeneous combination of pink and tan, often blending into the surrounding tissues.

The oculocardiac reflex may be used at this time to the advantage of the surgeon. With the anaesthetist alerted, the surgeon applies traction to the suspected structure. If a significant bradycardia or dysrhythmia results, the surgeon can be sure the suspected structure is extraocular muscle, especially if it is reproducible. In a previous study of over 600 extraocular muscles³ we found that 48% of the muscles receiving traction displayed a dysrhythmia or bradycardia exceeding 10%. The medial rectus muscle displayed a positive response in 57% of cases. If traction of the suspected muscle results in no significant change in heart rate, however, the structure may still be an extraocular muscle that simply does not stimulate the vagal pathways significantly.

Before an operation for a slipped muscle the surgeon must instruct the anaesthetist to avoid the use of a parasympatholytic agent, such as atropine, given intravenously at the time of induction or during operation. Atropine and similar agents given intravenously inhibit or abolish the oculocardiac reflex, whereas these drugs given intramuscularly before operation do not have this effect.

To abolish the elicited reflex the surgeon and anaesthetist have a choice. If traction on the extraocular muscle is released, the heart beat usually reverts to normal. In the unusual circumstance of bradycardia or dysrhythmia continuing after traction is released, atropine given intravenously will generally restore the heart to a normal rhythm.

It is interesting that, despite the number of previous eye operations (6 in case 1, with 2 on the muscle that slipped), or the duration of time since the last eye operation on the dislodged muscle (6 years in case 2), one may still elicit the oculocardiac reflex.

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Rift Valley fever ocular manifestations: observations during the 1977 epidemic in Egypt

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SUMMARY Ocular manifestations resulting from Rift Valley fever (RVF) virus infection were studied during an extensive RVF epidemic in Egypt during 1977. Colour photography and fluorescein angiography of 7 serologically diagnosed patients showed the commonest manifestations to be macular, paramacular, and/or extramacular retinal lesions, often occurring bilaterally. Haemorrhage and oedema were frequently associated with the lesions, and vasculitis, retinitis, and vascular occlusion were also observed. Patients were monitored during a 6-month convalescence, and, though resorption of the lesions occurred, approximately half the patients experienced permanent loss of visual acuity. Ocular disease was one form of the clinical spectrum of RVF; acute febrile, encephalitic, and fatal haemorrhagic RVF illnesses were also observed during the epidemic.

Rift Valley fever (RVF) is an arthropod-borne viral disease primarily affecting domestic animals with occasional involvement of man.¹ Before 1975 RVF in man was described as a mild, dengue-like, febrile illness.²⁻⁴ However, a report by Van Velden *et al.*⁵ described 4 human RVF fatalities and 1 case of retinitis during an RVF epizootic in South Africa in 1975. A number of earlier studies had reported ocular complications in suspected RVF patients.⁶⁻⁸ The general syndrome was one of macular and paramacular oedema with exudate-like lesions and haemorrhages. The most extensive report⁹ described 3 putative cases of RVF retinitis and 1 clinically indistinguishable case of tick-bite rickettsial fever retinitis. None of these previous reports included definitive diagnosis by virus isolation or the demonstration of serological conversion in paired acute and convalescent serum samples.

From October to December 1977 an extensive epidemic of an acute febrile illness occurred in the Nile Delta area of the Arab Republic of Egypt. Although the usual disease was an uncomplicated febrile illness, numerous cases of encephalitic, ocular, and fatal haemorrhagic disease were reported. The agent responsible for the febrile, encephalitic, and fatal haemorrhagic illnesses was RVF

virus.¹⁰ This report describes retinal lesions in patients infected with RVF during the epidemic.

Patients and methods

PATIENTS

From October to December 1977 an increased number of patients were referred to our clinic from an area in the Nile Delta 70 km north-east of Cairo (Sharqiya and Qalyubiya Governorates). They had similar clinical findings characterised by retinal-exudate-like lesions and haemorrhages. A study group of 7 patients representing the most frequently encountered lesions are presented in this report.

OPHTHALMOLOGICAL PROCEDURES

Ocular examination of all patients was performed by standard procedures, including an anterior segment examination with a slit-lamp and a fundus examination with the indirect ophthalmoscope. Clinical manifestations were photographed in all but the most severe cases, where a hazy view of the fundus often prevented clear photography. Fluorescein angiography was performed in the acute stage and at varying periods during convalescence.

SEROLOGICAL PROCEDURES

The methods of Casals¹¹ were used to treat serum samples, prepare RVF (Zagazig strain) viral antigen,

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Table 1 *Ocular findings in 7 RVF patients representing the variety of lesions observed during the epidemic. Patients were monitored for a period of 6 months*

Case	Initial examination	VA R	VA L	Convalescent examination
1	Macular exudate-like lesion with associated haemorrhage in right eye. Severe uveitis with KPs and vitreous haze	CF 50 cm	6/60	No improvement of VA; some resorption of exudate-like lesion
2	Mild macular exudate-like lesion in right eye	3/60	6/9	VA of right eye improved to 6/9; small paramacular scar remains
3	Paramacular exudate-like lesion in right eye	2/60	6/36	VA of right eye improved to 6/60
4	Macular and paramacular exudate-like lesions in right eye and paramacular exudate-like lesions in left eye	1/60	2/60	No improvement in VA of right eye; left eye improved to 6/36; some resorption of exudate-like lesions in both eyes
5	Macular exudate-like lesion with vasculitis and peripapillary choroidal ischaemia in right eye. Extramacular exudate-like lesions in left eye	1/60	6/9	VA improved to 6/36 in right eye
6	Bilateral macular exudate-like lesions with associated haemorrhages and severe bilateral vasculitis	1/60	CF 50 cm	No improvement VA of left eye; right eye improved to 6/36
7	Bilateral severe exudate-like lesions with haemorrhage; infarction-like areas in all quadrants. Severe uveitis with KPs and vitreous haze	No PL	No PL	No improvement of vision despite resorption of exudate-like lesions; vessels appear sheathed and occluded; optic atrophy occurred

VA=visual acuity. KP=keratic precipitates. CF=counting fingers. PL=perception of light.

and measure serum antibodies to RVF virus in the haemagglutination-inhibition (HI) and complement-fixation (CF) tests.

Results

All patients (Table 1) presented with a history of an acute febrile illness, usually of 3–4 days' duration, characterised by retro-orbital pain, headache, joint pain, and frequently by episodes of recurring fever. Visual symptoms developed 7–20 days after the onset of the initial febrile period.

When patients were seen soon after their febrile phase, acute and convalescent serum samples were obtained. A 4-fold or greater rise in HI or CF antibody titre between these paired samples confirms recent infection, and indicates the clinical illness was aetiologically related to the virus used in the test.¹² In a preliminary communication we reported 2 cases in which a 4-fold or greater rise in antibody titre to RVF virus established retinitis as resulting from RVF virus infection.¹³ As noted in Table 2, while only these 2 patients had a 4-fold increase in antibody titre during the observation period, all patients had greatly elevated HI and CF antibody titres to RVF virus.

In an area where RVF is endemic, the presence of antibodies to RVF virus in a single blood sample need not represent a response to a recent febrile illness. However, a retrospective serological survey of more than 700 blood samples collected before

1977 from people living in the Nile Delta was negative for antibodies to RVF virus, thus indicating the disease was not endemic in Egypt before the 1977 outbreak. Therefore, our patients from whom only 1 blood sample was obtained were assumed to have had an RVF virus infection just before their visit to our clinic since they: (a) had substantially raised RVF virus HI and CF antibody titres; (b) were geographically from the epidemic area; and (c) were seen during the epidemic period. Addi-

Table 2 *Haemagglutination-inhibition (HI) and complement-fixation (CF) tests for antibodies to RVF virus*

Case	HI antibody titre*		CF antibody titre*	
	First sample	Second sample**	First sample	Second sample**
1	160	1280	16	64
2	640	—	64	—
3	160	640	64	128
4	640	—	64	—
5	320	—	64	—
6	640	640	32	32
7	5120	5120	256	256

*The titre is expressed as the reciprocal of the maximum serum dilution yielding positive test results. **Obtained 1–2 months after the first sample.

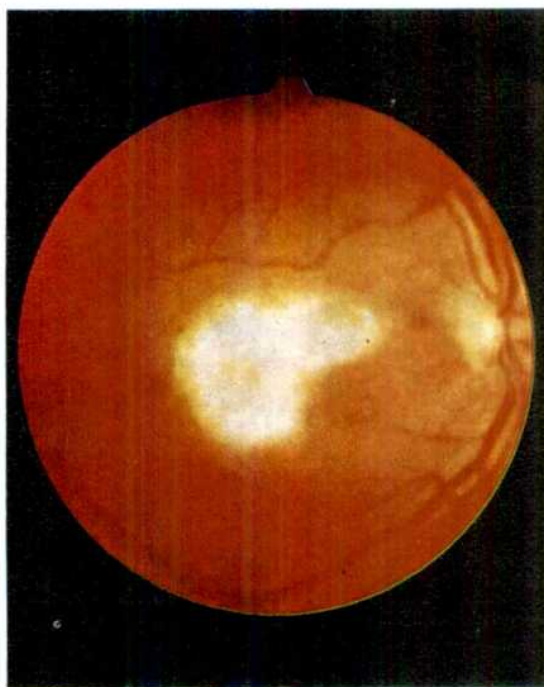


Fig. 1 (a) Photography of case 1 at the time of initial examination reveals an extensive macular lesion with haemorrhage and oedema

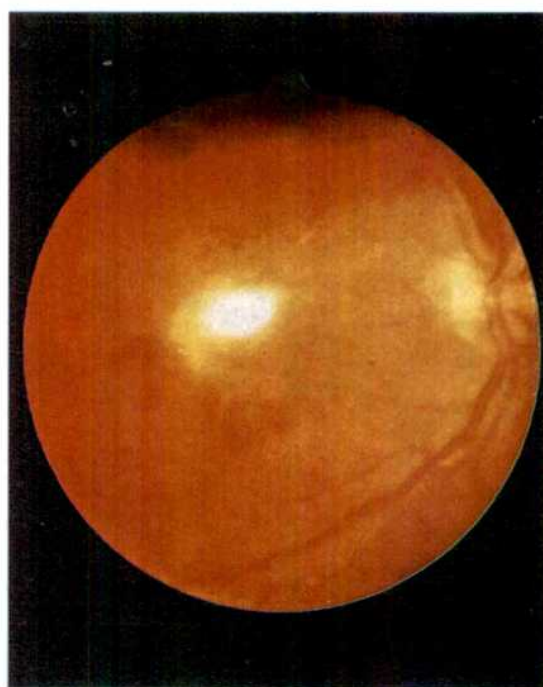


Fig. 1 (b) Examination of case 1 after 6 weeks shows partial resorption of haemorrhage, resolution of oedema, and partial resolution of lesion

tionally this group of patients was tested and found negative for raised levels of CF antibodies to selected rickettsial and viral agents which might cause ocular manifestations including Q-fever, measles, rubella, varicella, herpes simplex I, dengue I, and influenza type A, B, and C (data not shown). Thus we believe the ocular lesions seen in these 7 patients to have resulted from RVF virus infection.

Table 1 summarises the ocular findings in our study group of 7 cases and includes observations during a 6-month convalescent period. Each patient had either macular, paramacular, and/or extramacular exudate-like lesions. Unfortunately no tissues were available for histopathological studies, and it could not be determined if these lesions were truly exudates, or perhaps swollen and opaque cells, or axoplasm. For the purpose of demonstrating the major types of findings with this disease we have presented the 7 patients on the basis of their most illustrative clinical findings.

FINDINGS IN PATIENTS

Macular and paramacular lesions. Case 1 (Fig. 1) was a 50-year-old male whose macular lesion represented the type most frequently encountered (in both severe and milder forms) during the epi-

demic. The patient was seen 10 days after the onset of fever. Vision was reduced to counting fingers at 0.5 m, and the ocular examination revealed an extensive retinal lesion that could be seen through a vitreous haze. The lesion was roughly triangular, with the apex toward the optic disc, and retinal oedema and haemorrhages were present. The vitreous turbidity increased progressively over the next few weeks, and was associated with aqueous flare and fine keratic precipitates. Subsequent examinations at 3-week intervals showed marked resorption of the lesion (Fig. 1b), and only a macular scar remained 6 months later. No visual improvement occurred throughout the 6 month period.

Case 2 (Fig. 2) was a 26-year-old male who had a retinal lesion of a milder form consisting of oval, paramacular, exudate-like lesions associated with macular oedema, but without retinal haemorrhages. Nearly complete resorption occurred during the next 6 months with only a small paramacular scar remaining (Fig. 2d). Macular oedema completely resolved, and visual acuity improved from 3/60 at the initial examination to 6/9 after 6 months. The media were clear throughout the 6-month period. In the acute phase fluorescein angiography showed choroidal fluorescence to be obscured in the area

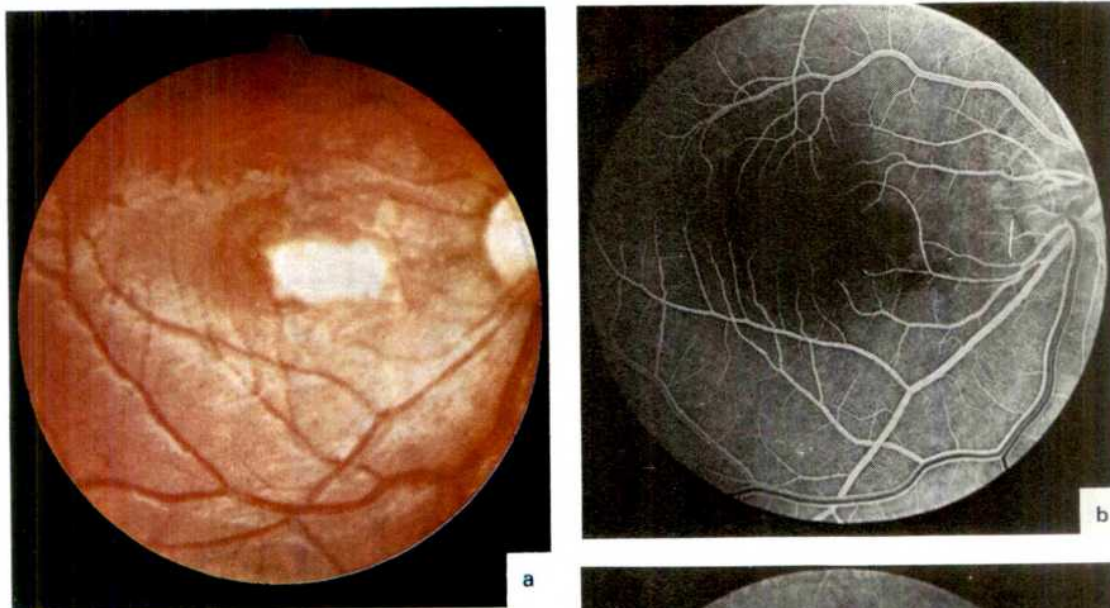


Fig. 2 (a) (b) (c) Photography and fluorescein angiography of case 2 at initial examination reveals oedema and a lesion bordering the macula

corresponding to the lesion. Figure 2b shows evidence of delayed peripapillary choroidal filling in the arteriovenous phase. Fluorescein angiography after 6 months showed a window defect at the paramacular scar and a residual delay in peripapillary choroidal filling (Fig. 2c).

Case 3 (Table 1) was a 51-year-old male with somewhat milder, paramacular, exudate-like lesions which completely resolved within 6 weeks.

Case 4 (Table 1) was a 52-year-old male with bilateral, paramacular, exudate-like lesions. Bilateral lesions were observed in the majority of cases seen during the epidemic.

Vasculitis and vascular occlusion. Evidence of vasculitis in the vicinity of the lesion can be seen in the fluorograms of case 2 (Fig. 2c). Additionally case 5 (Fig. 3) was a 53-year-old male with vasculitis which was not apparent on colour photography but was revealed with fluorescein angiography. Scattered macular, paramacular, and peripapillary exudate-like lesions were observed at initial examination. Some haemorrhages were also evident. The macular area was involved in the right eye (visual acuity 1/60), and the left eye had lesions bordering but not directly involving the macula (visual acuity

6/9). Fluorescein angiography revealed several minute vessels, particularly in the left eye passing from the disc toward the macula, from which dye leakage appeared to indicate vessel damage (Fig. 3c). Visual acuity improved to 6/36 during 6 months of convalescence.

Case 6 (Fig. 4) was a 52-year-old male who displayed extensive, bilateral, exudate-like lesions and haemorrhages at the posterior pole, with associated sheathing of vessels in an area near the left fundus. Fluorescein angiography showed evidence of widespread vasculitis and vascular occlusion (Figs. 4b and c) associated with extensive leakage in the late phase of the angiograms (Fig. 4d). Examination after

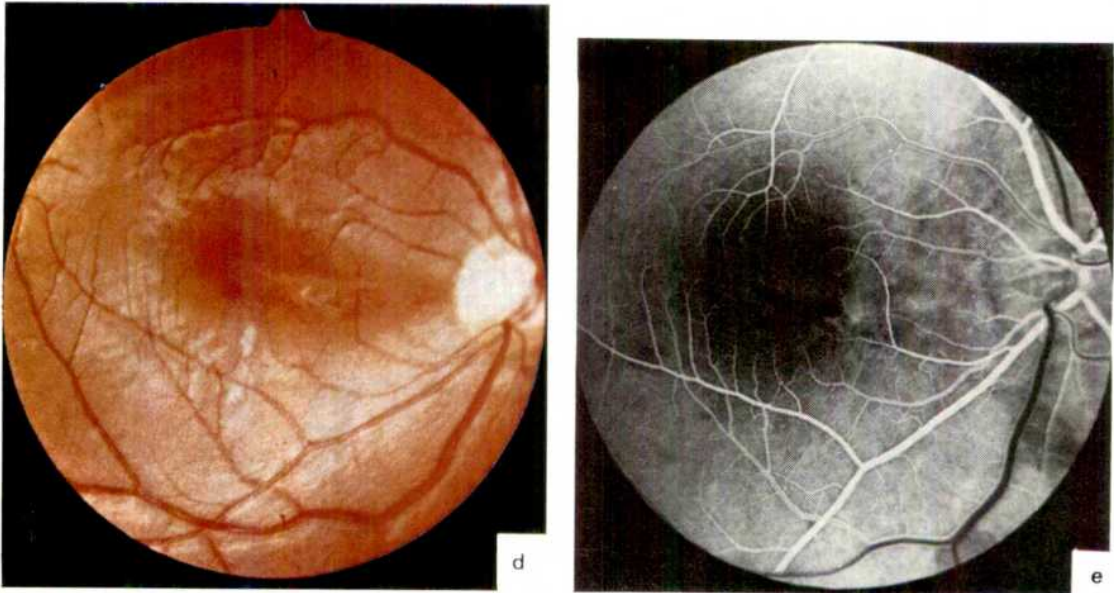


Fig. 2 (d) (e) Photography and fluorescein angiography of case 2 during an examination after a 6-month convalescence reveals resorption of the lesion and a remaining paramacular scar

Fig. 3 (a) Bilateral lesions seen at initial examination of case 5

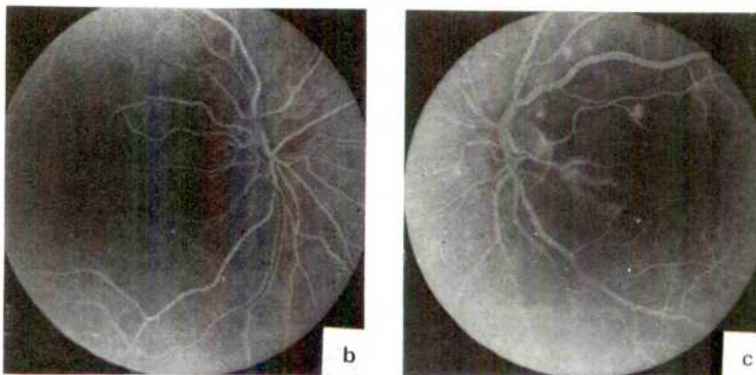
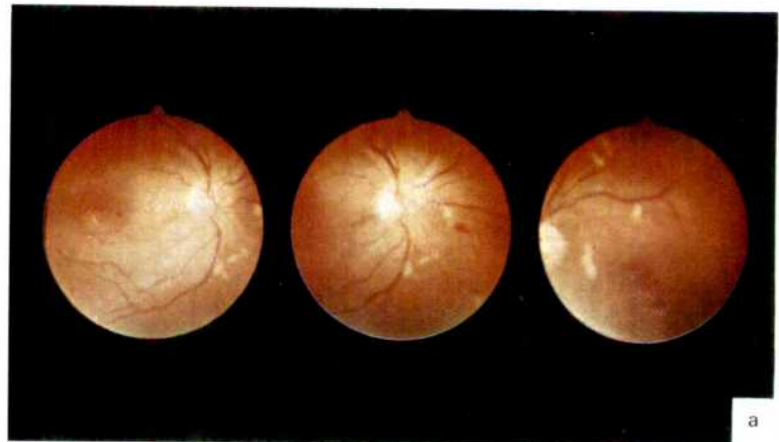
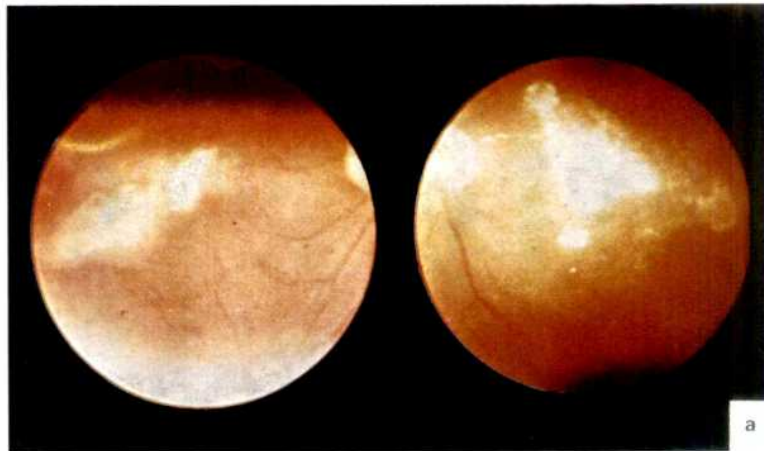


Fig. 3 (b) (c) Fluorescein angiography of case 5 at initial examination reveals extensive vasculitis

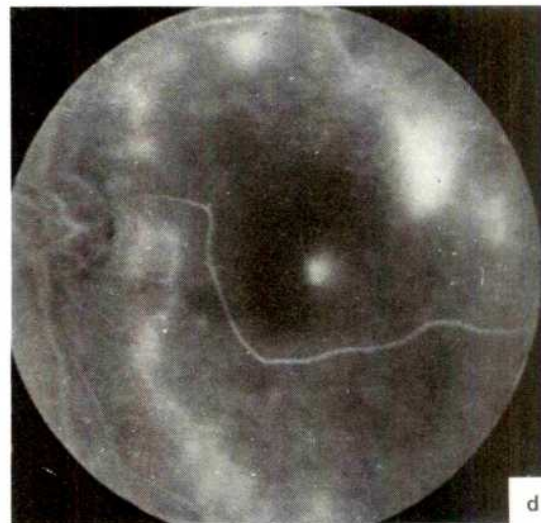
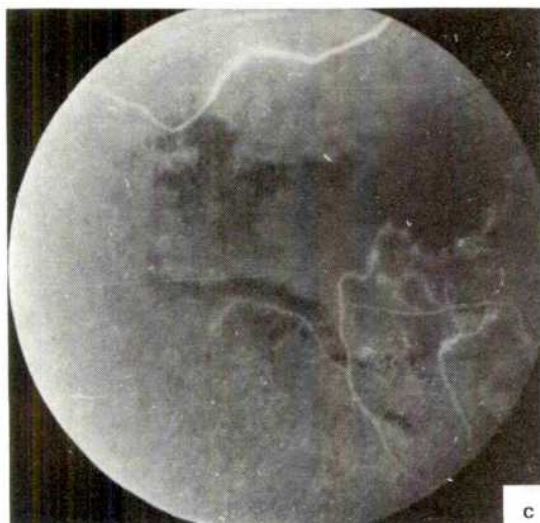
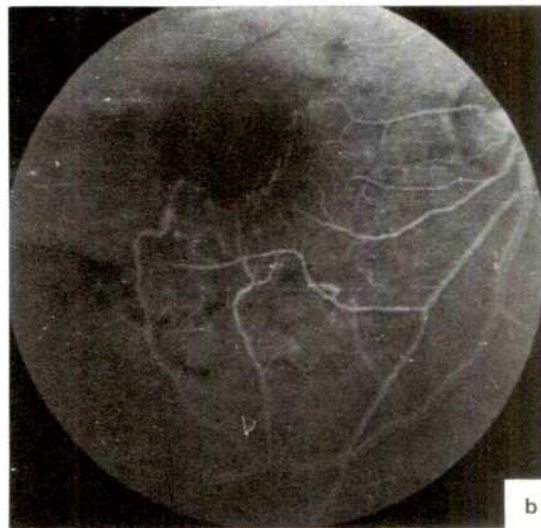
Fig. 4 (a) *Photography of case 6 at initial visit*



6 months showed improvement of visual acuity to 6/36 in the right eye but no improvement in the left eye. Almost complete resorption of the exudate-like lesions and the haemorrhages occurred during this period. Fluorescein angiography showed residual sheathed vessels with a general absence of macular vessels in the left eye.

Case 7 (Fig. 5) was a 55-year-old diabetic male who lost vision in both eyes after recovery from a 1-week episode of fever. Initial examination revealed extensive macular and paramacular exudate-like lesions with haemorrhages in both fundi. The retinal

Fig. 4 (b) (c) (d) *Fluorescein angiography of case 6 during initial examination reveals extensive vasculitis and sheathing of retinal vessels*



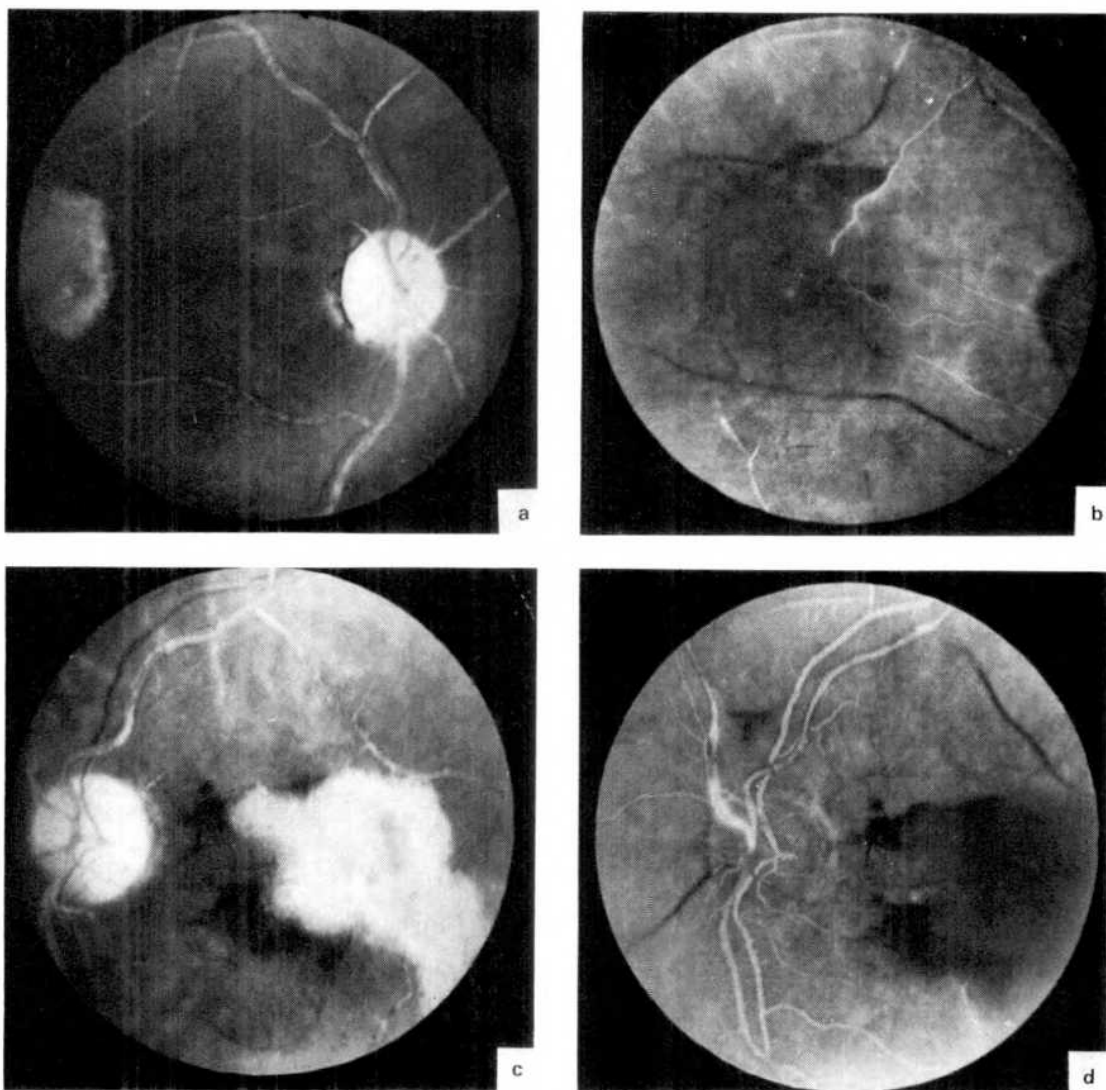


Fig. 5 Fluorescein angiography of case 7 at initial examination. Extensive lesions in both the right (a) (b) and left (c) (d) eyes are associated with vascular abnormalities

vessels of both eyes appeared sheathed. Fluorescein angiograms showed obscuration of the background fluorescence in the area of the lesions. In both eyes the vessels at the optic disc and macula appeared extensively damaged (Fig. 5).

Uveitis. A marked vitreous haze associated with aqueous flare and fine keratic precipitates was present in cases 1 and 7. However, there was no evidence of uveitis in the other 5 patients in the study group, and few cases of uveitis were seen

among the larger number of suspected RVF cases encountered during the epidemic. Clearing occurred slowly in these 2 cases, but no synechiae developed.

Discussion

Previous reports of RVF ocular complications have been limited. Gear *et al.*⁸ described a blurred vision syndrome in patients suspected of having RVF. Joubert *et al.*¹⁴ reported on a patient with retinal

haemorrhages and a second with retinitis and macular exudate-like lesions. Freed⁷ described a well defined, macular, exudate-like lesion in a putative RVF patient. Schrire⁸ reported on 5 suspected RVF cases with unilateral, macular, exudate-like lesions and 1 case with retinal detachment. Cohen and Luntz⁹ described 3 cases of RVF retinitis and 1 case of tick-bite fever rickettsial retinitis. Detailed fluorographic data in the latter report suggested vascular occlusion with primary involvement of the retinal circulation. However, the localised areas of retinal ischaemia and exudate formation were indistinguishable in the RVF and tick-bite fever (*Rickettsia conori*) disease. Consequently, diagnostic serological data must be cautiously interpreted, especially in an endemic RVF area. Easterday¹ reviewed the early literature and emphasised that the role of RVF virus in the aetiology of ocular disease was unresolved, since all previous diagnoses were made from 1 serum sample collected well after the onset of ocular lesions.

The present study further establishes that macular exudate-like lesions are indeed a complication of infection with RVF virus. However, unlike previous reports, bilateral lesions were frequently encountered among the patients seen during the epidemic, and in addition to macular lesions paramacular and extramacular lesions were also frequently observed.

The presence of vasculitis as well as retinitis most probably results in the development of the lesions. The severity of the lesions appeared to be related to the size and number of vessels affected. In cases of milder macular and paramacular lesions the minute vessels were involved. In the more severe cases retinitis, extensive vasculitis in larger vessels, and vascular occlusion probably contributed to the lesion. The delayed peripapillary choroidal filling observed in cases 2 (Fig. 2b) and 5 (Fig. 3b) during the arteriovenous phase may indicate choroidal involvement (other cases not included in this study appeared to show this more obviously, both in the peripapillary and macular area).

During the epidemic period we examined approximately 80 patients from the outbreak area with what clinically appeared to be RVF retinitis. Cultural factors prevented collection of serum from each person, and usually only males sought medical assistance. However, a total of 22 patients were examined serologically, and each had raised HI and CF antibody titres to RVF. We are continuing to monitor many of these patients, and approximately 40–50% have permanent loss of visual acuity following the resorption of lesions.

The retinal complications of RVF presented in this report were one phase of the clinical spectrum

of RVF disease observed during the epidemic. Uncomplicated, dengue-like disease was the most prevalent clinical illness. However, fatal haemorrhagic-like disease and an encephalitic illness have also been seen as resulting from RVF virus infection.¹⁰ Owing to the extent of the epidemic definitive attack rates, incidence of complications, age and sex distribution, and other epidemiological statistics have not yet been determined. However, it has been estimated that morbidity was between 20 000 and 200 000 and mortality in excess of 600.

All previous RVF outbreaks have been geographically limited to sub-Saharan Africa¹ and predominantly affected domestic animals. Human disease was usually recorded during these epizootics, but was always described as an uncomplicated febrile illness. Before the Egyptian outbreak only 4 RVF fatalities had been reported despite the scientific observation of the disease since 1930. Consequently, the Egyptian outbreak represents the largest and most severe RVF epidemic yet recorded. The isolation of the virus in Egypt also represents the northern-most spread of the disease. The source of the outbreak has not been determined, but the occurrence of a RVF epizootic in the Sudan in 1973¹⁵ raises the likelihood that the virus could have been introduced into Egypt from the south by infected camels or other livestock.

The unusually wide vertebrate and invertebrate host range of RVF virus probably has contributed to its spread. The virus now circulates in a variety of ecological settings in a 7000 km north-south range across Africa. The possible continued spread of RVF virus within Africa, as well as to other continents is a distinct possibility of which medical personnel should be cognisant.

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Congenital nystagmus among the Red-skins of the Highlands of Papua New Guinea

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SUMMARY Sixty-four people with pigmentary anomalies of the skin were examined in the Eastern Highlands of New Guinea. Thirty-one had a bronze-red skin colour which appears to be unique to New Guinea. Eighteen of the Red-skins had congenital nystagmus which was not associated with impairment of visual acuity. The fundi were normal. The pigmentary anomaly is recessively inherited, and the gene responsible for the nystagmus appears to be associated with those controlling skin colour. The condition appears to be a unique form of albinism and confers no disadvantage on those who have it.

It has long been known that among the indigenous people of New Guinea live a small number of individuals whose skin pigmentation is strikingly different from that of their fellows. D'Alberty¹ described his observations during the course of an epic navigation of the Fly river deep into the interior in 1871-3 as follows: 'A great surprise was however in store for me. Presently, a man walked in as the others had done, armed and adorned with flowers and necklaces, like them but accompanied by a son of about 25 and a daughter of about 20, both of them were albinos. Their hair is whitey-brown, their eyes blue and their skin white, like that of Europeans'.

Mikloucho-Maclay,² who explored the coast east of the Eastern Highlands near Madang from 1871 to 1883,³ noted 'albinism— $\frac{1}{2}$ albinism not rare'.

The earliest observation of light-skinned people in the Eastern Highlands themselves appears to have been made by one of the first explorers, Dr H. F. W. Bergmann, a missionary who entered the region in 1929 (Sentinella, personal communication). In his as yet unpublished book he says: 'Nearly everywhere in New Guinea, almost in every tribe, there are some so-called albinos. Amongst the Kamanuku and the surrounding tribes there are also a few of them but not very many. The skin of these people is quite light coloured, nearly a reddish-white. Also the eyes have less pigment and are sensitive to light. The colour of

them varies, some are very light, others are only a bit light. The hair is mostly red or reddish-white. The skin is mostly full of freckles . . . Each tribe knows that such people are there and find it quite normal. They call them kuruo, which we must translate with white or yellow-white or yellow-red'.

This description obviously includes light-skinned individuals other than albinos. A specific distinction is made by Vogel,⁴ who went to New Guinea in 1950, and on his way to investigate the Jimmi River pygmies he noted that at Meguagi there were 'several people the colour of whose skin was quite different to that of the majority. Their complexion was very light, reminiscent of ours when we are slightly sunburnt. On the whole the appearance of these people is the same as all the others, except that their curly hair is more brown than black, in certain cases bordering on fair. I had also observed such oddities in the Wahgi valley. They are not albinos . . . '.

It is interesting that he did not see any light-skinned individuals among the pygmies.

It is now agreed that there are four easily distinguished types of skin pigmentation among the New Guineans: black (typically Melanesian), red, pale brown, and white (the true albino).^{5,6} Red-skins have recently attracted particular attention from geneticists and biochemists because they appear to be unique to New Guinea. In the Eastern Highlands they account for approximately 2% of the population, and the determining gene behaves as an autosomal recessive.⁶ The precise origin of the skin colouration has not been established. It is not a result of dietary deficiency, since the nutritional state of the population has been reported on,^{7,8}

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and there is no evidence that that of the Red-skins is different from that of the black Melanesians. There is some evidence that the melanocytes of the Red-skin are morphologically distinctive and that the red colouration may be due to the presence in the epidermis of a phaeomelanin.⁹

These investigations into the nature and inheritance of the pigmentary anomaly of the Red-skin have not been accompanied by a detailed clinical description. While we and others have noted that nystagmus occurs in an appreciable proportion of the Red-skin group,⁵ the data on visual function are fragmentary. We report here the results of a clinical study carried out in the Goroka district of the Eastern Highlands.

Subjects and methods

Hamlets and villages were visited in the Asaro and Bena Bena valleys and in the Lufa subdistrict and inquiries made as to whether there were any individuals there with unusual pigmentation. Examination was carried out either in the Institute of Medical Research in Goroka or in a clinic temporarily set up in Lufa. A family with a sibship of 8, of whom 4 were albinos, was examined in Madang.

Skin, hair, and iris colour were recorded. Visual acuity was ascertained with a Snellen chart, and colour vision was tested with the American Optical Society's pseudo-isochromatic plates (Hardy—Rand—Rittler). The fundi were examined by direct ophthalmoscopy and photographed in selected cases. Initially all subjects were examined with dilated pupils, but since this caused distress because of the bright ambient light most later subjects were examined with pupils undilated. The eye movements and pupils were examined and a general neurological assessment was carried out.

Results

SKIN COLOUR

Previous investigations have established an incidence of 1.5–2% of Red-skins in the Goroka district.^{5,6} We examined 64 individuals (some of whom had been included in Harvey's survey), who were readily classified into 3 groups according to the appearance of the skin: *Red-skins*. Thirty-one individuals showed the characteristic bronze-red skin colour (Fig. 1). *Pale-skins*. Twenty-six individuals had skin of a uniform café-au-lait colour. *Freckled Pale-skins*. Seven individuals had very pale brown skins with darker freckles and were categorised separately. Freckling was not a feature of the Red-skins.

The hair colour ranged from very fair to black, and as noted by both Walsh⁶ and Harvey,⁵ there was a poor correlation between hair colour and the intensity of the reddish-brown skin pigmentation. It is nevertheless the case that natural fair hair is seen only among the 3 groups of subjects described here, together with the rare true albinos (Fig. 2), and not among the black Melanesians. However, ritual colouration of the hair with clay and bleaching with lime are common.

IRIS COLOUR

The normal iris colour of the black Melanesian is a deep uniform brown (Fig. 3). Somewhat more than one-third of the individuals with pigmentary anomalies had a variable amount of grey colouration in the iris. This finding was most marked and most frequent in the Freckled Pale-skins (6/7). Only one of these 7 had a uniform brown iris, 1 had a speckled grey-brown iris, and in the remaining 5 the iris was a uniform grey. Twelve of the 25 Pale-skins had a more or less grey iris: 5 were plain grey and 7 contained a mixture of brown pigment (Fig. 4). In contrast only 6 of 29 Red-skins showed any grey in the iris, and in all of these patches of brown pigment were obvious. Iris colour in the remainder was indistinguishable from normal (cf. Figs. 3 and 5).

TRANSLUCENCY

Albinism may be suspected when there is an increase in translucency of the iris in response to the application of a bright focal light source to the sclera. In our investigation we were restricted to the use of a bright pocket torch and examination in a darkened room. In the normal dark Melanesian in these conditions a faint glow was visible obliquely through the pupil, but there was no translucency of the iris. In the 25 Red-skins examined 6 showed iris translucency, 4 of these having grey iris colouration and 2 having brown irides. Nine of the 17 Pale-skins and 6 of the 7 Freckled Pale-skins showed an increase in translucency of the iris, which in each case showed grey colouration. Classical oculocutaneous albinos seen in Madang showed brilliant translucency of the iris, much more striking than any seen in the Highland groups (Fig. 6). The translucency observed in the Red-skins and Pale-skins was nevertheless abnormal and indicates hypopigmentation of the iris, similar to that seen in some forms of tyrosinase-positive oculocutaneous albinism.

NYSTAGMUS

The most frequent and striking abnormality was congenital nystagmus. In most patients it was present in the primary position, where it was usually



Fig. 1 *A Red-skin*



Fig. 2 *An albino child with his normally pigmented Melanesian parents*

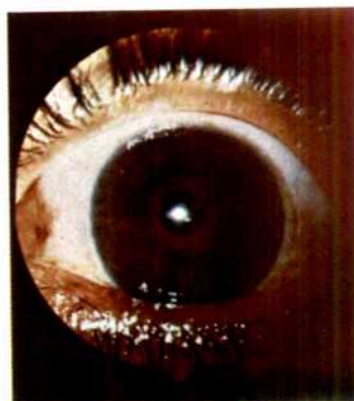


Fig. 3 *Iris of a normally pigmented black Melanesian*



Fig. 4 *Iris of a Pale-skin*



Fig. 5 *Iris of a Red-skin*

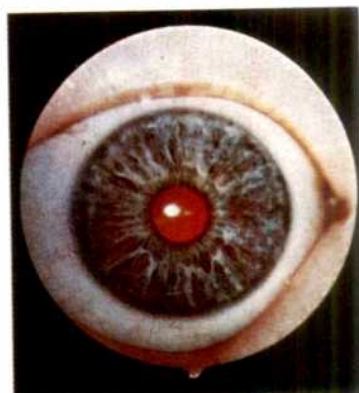


Fig. 6 *Iris of an albino showing striking translucency*

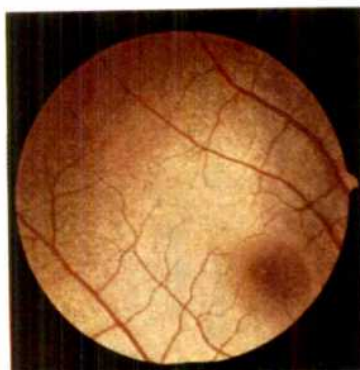


Fig. 7 *Macular region of a black-pigmented Melanesian*

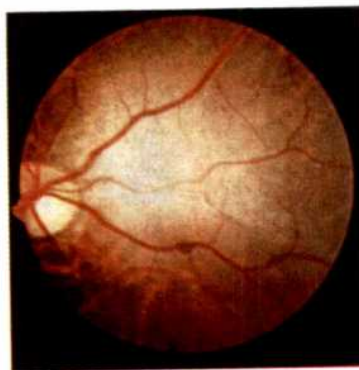


Fig. 8 *Fundus of a Red-skin showing a tigroid pattern*



Fig. 9 *Macular region of a Pale-skin*

pendular. Conjugate lateral gaze increased the coarseness of the nystagmus, which usually then took on a jerky component with the quick phase in the direction of gaze. On vertical upward and downward gaze the nystagmus remained in the horizontal plane. Optokinetic nystagmus was examined by means of a tape with alternating dark and light stripes. Satisfactory observations were made in 22 patients with nystagmus. We observed a normal optokinetic response in both horizontal and vertical planes in 3 individuals only. The horizontal response was absent in 12 and the vertical was absent in 5. The most common abnormality was a decrease in amplitude of the optokinetic response, more often in the horizontal than in the vertical plane, sometimes more marked in one direction of gaze than others. In individuals with nystagmus in the primary position vertical movement of the tape usually induced optokinetic nystagmus in an oblique plane. The null point for the nystagmus was usually eccentric, resulting in the adoption of a compensatory head posture. Titubation was present in a few patients.

The incidence of nystagmus in the patient groups is shown in Table 1. No example was seen in the control group. Overall, nystagmus occurred in 58% of those with pigmentary anomalies of the skin. Comparison of the incidences between groups showed a marginally significant difference only between the Pale-skins and the Freckled Pale-skins ($\chi^2=4.93$, $P=0.025$), but the numbers are too small to draw firm conclusions.

VISUAL ACUITY

The visual acuity was measured in 49 subjects, including 33 of the 34 with nystagmus. Ten had abnormal acuities, 1 without nystagmus having a retinal detachment. In the remaining 9, all with nystagmus, the acuity deficit was unilateral in 2 (1 of whom had a concomitant strabismus on the affected side). Of the remaining 7, 5 had 6/9 vision in one (1) or both (4) eyes. Except for the subject with strabismus, the mechanism of impairment was not established, although 1 patient had opacities in the media. The optic discs were normal in all. The retinae and maculae were examined through

dilated pupils in 3 of the subjects in the group with nystagmus. All were normal (see below).

Since there was no impairment of acuity in 24 of the 33 subjects with nystagmus examined and in 7 of the remainder the impairment was unilateral and/or mild (visual acuity 6/9 or better) it is obvious that the occurrence of nystagmus is independent of acuity impairment. The overall results show that Red-skins, unlike classical oculocutaneous albinos, do not show a constant association between the pigmentary anomaly of the skin and impairment of acuity.

FUNDI

The fundi were examined in 45 subjects, 18 with the pupils dilated. Thirty-three of the 34 patients with nystagmus were examined, 10 through dilated pupils. A satisfactory assessment of the peripapillary retina could be made in 19 of the undilated subjects with nystagmus. In the dilated subjects a thorough examination of disc, macula, and retina was possible. In all subjects the optic discs were normal. The retinal pigmentation in the 3 abnormal skin-colour groups (with and without nystagmus) was indistinguishable from that of black Melanesians, of whom 30 were examined in the present study and many hundreds of whom have been examined by R. W. H. in the course of 10 years of neurological work in the New Guinea Highlands. The retina itself tended to be somewhat darker than that of Europeans (Fig. 7) and frequently had a tigroid pattern (Fig. 8). The maculae were normal (Fig. 9). Abnormalities were found in 2 subjects only. One patient without nystagmus had a retinal detachment and one patient with nystagmus (but a normal acuity) showed retinal colloid bodies. The normal appearance of the retinae in the Red-skins, Pale-skins and Freckled Pale-skins contrasted sharply with that of the 4 oculocutaneous albinos seen in Madang, all of whom had typical albinoid fundi.

COLOUR VISION

Colour vision was tested in all those old enough to co-operate (50). No abnormality was detected, except in the single eye with retinal detachment, in which the acuity was less than 6/60.

AGE, SEX, AND ETHNIC GROUP

Nystagmus was seen in subjects of all ages from 2 years to over 50 (the age of older New Guineans is not usually known accurately). The 5 language groups (Gahuku, Bena Bena, Asaro, Yagaria and Chimbu) were all represented. Table 2 shows the sex distribution of the pigmentary anomalies and nystagmus. There was no significant difference in the incidence of nystagmus between males and

Table 1 *Incidence of nystagmus*

<i>Skin colour</i>	<i>No. examined</i>	<i>No. with nystagmus</i>
Red	31	18
Pale	26	10
Freckled pale	7	6
Total	64	34

Table 2 Relationship between sex*† and incidence of nystagmus

	Males	No. with nystagmus	Females	No. with nystagmus	χ^2
Red-skins	18	12	11	5	1.27 NS
Pale-skins	14	7	10	3	0.96 NS
Freckled pale-skins	3	3	4	3	NS‡
Total	35	22	25	11	2.10 NS

*There was in addition one hermaphrodite Red-skin with nystagmus.

†The sex was not noted in 3 further subjects. ‡Fisher's exact test, $P=0.57$.

Table 3 Relationship between sex and Red-skin anomaly

	Red-skins	Others	Total
Male	17	18	35
Female	14	11	25
Total	31	29	60

females in any group. The difference in frequency of males and females in the Red-skin group was not significant either (Table 3: $\chi^2=0.323$; $P=0.58$).

Discussion

Congenital nystagmus occurs in association with anomalies of skin and iris pigmentation in the Eastern Highlands of New Guinea. Previous surveys have reported an incidence of 1.5–2% of Red-skins,^{5,6} and in 2 villages near Maprik, with a population of 553, the incidence reaches 3.8%. The present investigation has shown that approximately two-thirds of such individuals have nystagmus—a remarkably high incidence in comparison with European populations.

The Red-skin colour is inherited recessively.^{5,6} The mutation rate must be very low, since although Red-skins are widespread in the Highlands and we have seen them in the Gulf of Papua and in the Sepik (but not on Kar Kar Island), they have not been identified outside Papua New Guinea. An incidence of 2% is high for a recessive condition and indicates that neither the pigmentary anomaly nor the nystagmus confers a disadvantage for survival on the affected individuals. Such a situation could result from a selective advantage of Red-skins in infancy in areas of high infant mortality. This explanation would account for the remarkably high gene frequency.⁶ An additional factor contributing to the high frequency of the Red-skin gene may be a social one: Red-skins are much sought after as wives.

The circumstances of the albino are quite differ-

ent. The extreme photophobia and the poor acuity dictate a pattern of life different from that of other New Guineans: the albino spends the day indoors or in the shade and takes little part in tending the gardens and hunting. Despite these precautions, the incidence of basal cell carcinoma of the skin is high in albinos. Neither in the present investigation nor in that of Walsh⁶ has a single example of skin cancer been seen among the Red-skins. Although we did observe some photophobia, it did not interfere with the normal activities of the Red-skin.

It is clear from our investigations that the gene responsible for the inheritance of nystagmus is closely associated with genes controlling eye and skin colour. More detailed family studies are required to establish whether the same or separate genes are involved.

Finally, the question arises whether the Red-skins should be regarded as having a form of albinism. Witkop¹⁰ adopts a broad definition of albinism as 'a hereditary defect in the metabolism of melanin, resulting in a decrease or absence of this pigment in skin, mucosa, hair or eyes'. Although histological observations suggest that there may be some reduction in the overall amount of melanin in the skin of the pale brown individual and a small reduction in the Red-skin,⁹ quantitative data are lacking and the evidence is not conclusive. The ocular abnormalities of the Red-skin differ in some respects from those of the albino. Whereas in albinos nystagmus is invariable and is always associated with impaired acuity, nystagmus is absent in one-third of Red-skins and when present is unrelated to acuity. Iris translucency is striking in the oculocutaneous albino but is infrequent and of relatively minor degree in the Red-skin. Finally the fundus of the Red-skin is ophthalmoscopically normal. These differences are, however, a matter of degree, and we conclude that the Red-skin anomaly falls within Witkop's definition of albinism and represents a unique form of it.

We are grateful to E. H. O. King and A. McGregor for assistance in the field, to Dr M. Barraitser, Dr D. A. S. Compston, Mr Barrie Jay, and Dr S. Sergeantson for advice, and to Professor Barrie Jones for the loan of equipment. We are indebted to Mr C. L. Sentinella, editor of the Mikloucho-Maclay Diaries, for his generous help in identifying early references to albinos and Red-skins in Papua, New Guinea.

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Book reviews

Advances in Ophthalmology. Vol. 40. Eds. M. J. ROPER-HALL, H. SAUTTER, E. B. STREIFF. Pp. 224. DM188. Karger: Basle, Switzerland. 1980.

This volume gives information on three diverse subjects, namely, the causes of blindness throughout the world; the proteins in the aqueous humour; and the standardization of visual field testing. The first report emphasises once again the problem of even finding a uniform definition of blindness and the difficulties of obtaining reliable statistics. There are, however, some useful tables which give a guide to the widely differing problems in many countries. The second report is a very useful general account of how proteins may enter the anterior chamber and the extensive work of analysis on which the author has been engaged for many years. It ends with an extensive bibliography and is thus a most useful account of this subject. The final report was commissioned by the National Research Council of America. It gives an account of the basic factors in visual field testing. It does not make any particularly new recommendations but is useful in that it summarises the well known facts about field testing which have been contributed by others as well as American authors.

R. F. FISHER

Textbook and Atlas of Slit Lamp Microscopy of the Living Eye. Vol. 2. By Alfred Vogt. Pp. 422. DM600. Wayenborgh: Bonn, W. Germany. 1979.

This is an English translation of volume 2 of the incomparable textbook and atlas published by Vogt in 1931. The excellence of the original colour drawings and black-and-white photographic illustrations has been fully maintained. For anyone wanting an excellent translation of the foundations of slit-lamp examination of the lens and zonule this volume is obligatory. Since the subject matter consists mainly of descriptive observations, the volume is by no means dated and is thus a worthwhile book of reference. I am afraid, however, its high price will prevent its purchase by many ophthalmologists.

R. F. FISHER

Vitreoretinal Disease. By PETER H. MORSE. Pp. 625. £51.00. YB Medical Publishers: London. 1979.

This book details the experience and interests of the director of the Retinal Service in the Pritzker School of Medicine in the University of Chicago. The title is misleading, as more than half the book is concerned with retinal conditions which have no vitreous implications whether by causation or complication. Although most 'medical' retinal conditions are adequately documented, this aspect of the book compares unfavourably with a recent alternative text on retinal and choroidal diseases from the Pritzker School.

Readers expecting a truly vitreoretinal manual will find the sections on vitreous surgery and previtrectomy assessment disappointingly short, with only half a page of

text devoted to ultrasound examination, and virtually no discussion of multiple-incision/common-gauge surgery, which is the current vogue. The most valuable part of the book is that third which is devoted to the assessment and treatment of rhegmatogenous retinal detachment. The author describes in great detail the preoperative, operative, and postoperative management of patients, discussing both the 'buried implant plus diathermy' as well as the 'explant plus cryotherapy' methods of treatment. However, the almost missionary zeal with which measures to improve patients' comfort and wellbeing are advocated sometimes blurs the issues; for example, the chapter on 'scleral buckling techniques' begins with 2 paragraphs on straps—not of the encircling silicone variety but the heavy leather type securing the patient to the theatre trolley or operating table. Technical instructions also tend to be unduly fastidious—the foot-pedal (for cryotherapy) should be placed near the surgeon's foot—while the diagram of treatment of a retinal tear implies that double freezing of the bare pigment epithelium within the break is desirable. The description of giant breaks also compounds the continuing confusion about this topic among retinal surgeons.

Overall, the book is well written but is only modestly illustrated and is somewhat lacking in direction. The section on 'macular pucker', for example, is relegated to a 'miscellaneous conditions' chapter near the end of the book (nestling uncomfortably between 'photoreceptor degeneration and cancer' and 'retinal haemorrhage in the newborn') and includes no mention of surgical treatment. Each chapter ends with a bibliography, whose usefulness is limited by the virtual exclusion of non-American publications and the absence of any referencing system within the text itself. DAVID MCLEOD

Vitrectomy. 2nd edn. By ROBERT MACHEMER and THOMAS M. AABERG. Pp. 262. \$23.50. Grune and Stratton: New York. 1979.

In the second edition of this book Dr Machemer has been joined by Dr Aaberg. The authors state that the book is not intended to be an encyclopaedia on vitrectomy but a presentation of the personal experience of the 2 authors. The fact that this edition is considerably larger than the first reflects the rapid advances that have been made in this field of microsurgery during the last few years. The indications and contraindications for vitrectomy are continually changing. Disorders such as diabetic retinopathy with severe rubeosis iridis and retinal detachments complicated by severe periretinal proliferation, which were previously considered inoperable, may now benefit from surgery.

Despite the addition of much new material and an expansion of the bibliography, this edition has a logical sequence and is easy to read. The first few chapters deal with the selection of patients, the rationale for treatment, and preparation of instruments. The emphasis of the book is very much on surgical techniques. All the new techniques such as the removal of epiretinal membranes, fluid-gas exchange, and transvitreal cryotherapy and drainage of subretinal fluid are described in detail and

amply illustrated. For those who do not wish to become involved with the complicated and delicate manoeuvres within the vitreous cavity there is an excellent section on the use of vitrectomy instruments in anterior segment disorders. Of particular interest is the treatment of pupillary membranes and the management of neovascular glaucoma by a filtration procedure over the pars plana.

This is one of the best of many books on vitrectomy that have recently appeared on the market and is strongly recommended.

J. J. KANSKI

Real Time Ophthalmic Ultrasonography. By S. N. HASSANI. Pp. 214. DM69. Springer-Verlag: Berlin. 1978.

This book describes contact B-scanning of the eye and orbit with the Bronson Turner B-scan unit and is written by 2 radiologists. One of the authors' presumed intentions was to orientate the nonophthalmically trained examiner to ocular anatomy, pathology, and therapy. Unfortunately much of the book reads like a student's hectic jottings from some out-of-date ophthalmic text, and ophthalmologists will wince at the wealth of confusing statements, inaccuracies, and frank errors. A few examples might be cited: the cross-sectional diagram of the eye implies that the vitreous is richly vascularised; another diagram labels the posterior lens capsule 'anterior capsule' and presents a novel interpretation of the site and configuration of the ciliary body; there is no description of the ora serrata, which, to judge by the diagrams, enjoys an enormously diverse anatomical position; the optic nerve is described as having an S-shaped curve. Furthermore, little priority is given to those aspects of ophthalmology likely to be encountered in an ultrasonic department. In the section on systemic hypertension, for example, the retinopathy is described but there is no mention of the commonest ultrasonic presentation, that is, vitreous haemorrhage and incomplete posterior vitreous detachment arising from retinal branch vein occlusion complicated by neovascularisation. This curious disorientation is most evident in the glossary of ophthalmic terms at the end of the book. For some reason, 'anomalous retinal correspondence', 'cyanosis retinae', 'snow blindness', and 'Hallerman-Streiff syndrome' are considered worthy of definition, but there is no mention (anywhere) of the 'vitreous base', 'giant retinal tear', or 'massive periretinal proliferation'.

There are approximately 400 B-scan photographs covering a wide range of pathology. Again, there is a curious imbalance in emphasis—there is no clear illustration of a 'collar stud' choroidal melanoma, a diabetic traction detachment, or an optic nerve tumour. Yet there are dozens of pictures of normal extraocular muscles and cataractous lenses, 9 examples of asteroid hyalosis, and, unbelievably, 5 pictures of so-called 'reflection artefacts' arising from faulty camera technique. The labelling of B-scans also leaves much to be desired—sheets of echoes in the posterior vitreous are labelled 'macular oedema', 'retinitis', and 'diabetic retinopathy', and many archetypical ultrasonic findings are confused—for example, cyclitic membrane versus posterior hyaloid

membrane and 'organised' haemorrhage versus retrohyaloid debris. Occasionally the figure legends indicate one disorder and the labelling on the B-scan indicates another.

Even the introductory chapter on the 'Principles of ultrasonography' contains many incorrect statements, highly confusing diagrams, and spelling mistakes.

In the foreword close co-operation between the ophthalmologist and the ultrasonographer/radiologist is recommended. Sadly, this book demonstrates many of the pitfalls which arise when such liaison is lacking. In view of the recent flurry of books on ophthalmic ultrasound, it is difficult to imagine any ophthalmologist, radiologist, or ultrasonographer who might benefit from reading this one.

M. RESTORI

D. MCLEOD

A Guide to Medical Photography. Ed. PETER HANSELL. Pp. 163. £17.95. MTP Press: Lancaster. 1979.

Peter Hansell has edited the work of eight other authors from various countries and contributed 1 chapter himself to complete this attractive book on medical photography, a subject about which there are very few other textbooks. It is a nicely produced and very well illustrated volume, which will serve to show the ophthalmologist what is possible in medical photography and so may help him in preparing material for teaching and publication.

There is just 1 chapter on ophthalmic photography, by Phillip Hendrickson of Alabama, USA, in which he has to encompass the entire scope of his subject in just 10 pages. An ophthalmologist wishing to apply photography to clinical or research purposes, such as in the fields of fluorescein angiography and slit-image photography, will not find sufficient information to allow him to become proficient in this work. But a reasonable number of references are provided for those willing to progress beyond the scope of this book.

NICHOLAS PHELPS BROWN

A Colour Atlas of Ocular Tumours. By MICHAEL A. BEDFORD. Pp. 78. £12.00. Wolfe Medical Publications: London. 1979.

This is an excellent book which provides comprehensive photographic recordings with accompanying short factual accounts of the various benign and malignant tumours which involve the skin of the eyelids, the conjunctiva, the uvea (iris, ciliary body, and choroid), and the retina.

In any medical textbook the question of illustrations is a vexed one because it involves inevitably a compromise between providing a comprehensive photographic account of the various diseases, which frequently must be in colour to be effective, and providing a book which is economically viable. Sometimes illustrations may be reduced to a minimum, so that a factual text is achieved at a reasonable cost. As the late Sir Stewart Duke-Elder said, 'Live pictures should be available in the clinic'. This is appropriate when the book is confined largely to

a description of routine ocular conditions which can be viewed readily in the outpatient department, but it does not apply to specialised conditions like ocular tumours, and, as stated in the introduction to this book, the relative infrequency of many of these tumours precludes the average eye surgeon from becoming familiar with them, particularly during the various stages of their development. Such knowledge is essential in making an early diagnosis, which is so important in any form of malignant disease.

This book fulfils a great need, and the standard of the illustrations is extremely high. The short comments are entirely complementary to the illustrations. There is a fair balance between the roles of surgical treatment and modern methods of irradiation in the management of many of the conditions.

Relatively few criticisms need be made, but there is some confusion about the management of surface melanomata. The book indicates that a flat surface malignant melanoma may be treated by beta irradiation whereas a raised lesion should be treated by exenteration, though it is possible that this advice is limited to the fornices and the palpebral surfaces of the eyelids. In fact, however, it is extremely rare for a surface melanoma to assume malignancy without becoming elevated (a possible exception is cancerous melanosis of the eyelid—the lentigo maligna of Hutchinson). Indeed a junctional naevus is elevated in the absence of proved malignant change, so that elevation of a lesion is a doubtful means of determining the precise nature of the lesion and, therefore, the most effective method of its treatment. Exenteration is the essential measure in certain cases, but as a general rule irradiation should be carried out as a primary procedure, and a 'flat' surface which is appropriate for beta irradiation can be achieved when the bulk of the lesion is removed for biopsy.

The other criticisms are only trivial. Fig. 13 is to the left (rather than above) Fig. 12, and proper recognition should be made of George Coats, who contributed so much to ophthalmology in the relatively short age span of 39 years, by placing the apostrophe in the correct place, so that Coats's disease is not correctly described as Coat's disease, though to be less pedantic Coats' disease may suffice.

This book should be of distinct value to the practising ophthalmologist who sees cases of malignant disease of the eye infrequently.

KENNETH WYBAR

Colour Atlas of Ophthalmology. By ARTHUR LIM SIEW MING and IAN J. CONSTABLE. Pp. 151. £5.00. Henry Kimpton: London. 1979.

This is a useful little pocket-book designed primarily for general practitioners, medical students, and paramedical personnel rather than the ophthalmologist proper. Published in Singapore, it contains some 190 colour illustrations, mainly well reproduced and of good variety. From the photographic aspect the inadvisability of using a ring-flash for close-ups of the external eye is apparent in several examples, but by and large the standard is high. The subject matter is logically covered in 11 chapters and includes sections on examination of

the eye and refraction. Indexing is adequate, and the price is reasonable. The few minor and easily corrected errors do not detract generally from the potential usefulness of this book.

PETER HANSELL

Medical Examination Review, Ophthalmology: 1630 Multiple Choice Questions with Answers. By H. N. YADAV and ASHOK PRAKASH. Pp. 206. £2.40. Prakash Publication: Darbhanga, India. 1979.

This paperback contains 1630 multiple choice questions, with answers in the last pages of the book, designed for undergraduate and postgraduate medical students. Their basic objectives are stated openly in the preface to be 'to reasonably master over the subject, to reproduce the knowledge in the examination and to get a suitable job through various competitive tests'.

The book would have been improved by a separate grouping of the questions into those suitable for the undergraduate, the postgraduate, and for both. I suspect that most British examiners would think that many questions were unsuitable for either. There is a surprising tendency to expect precise numerical answers, for example,

Sex incidence of dacryocystitis:

A 60 : 40 M : F

B 50 : 50 M : F

C 40 : 60 M : F

D 30 : 70 M : F

E 20 : 80 M : F

(E is the answer given)

or precise semantic knowledge. I have never met 'madarosis' and 'tylosis' used other than facetiously outside the covers of encyclopedic works. Candidates are expected to know the identity of eponymous structures like Hannover's, Sondermann's, and Petit's canal. I wonder how many experienced ophthalmologists who take a careful history would agree that refractive errors are a contributory or aggravating factor in migraine?

The MCQ seems to me to be less objective than its supporters claim—granted that fair assessment of an essay answer is not at all easy. Compiling a satisfactory MCQ is a very difficult art, and these authors are to be commended for making a brave attempt. However, we must continue our efforts in medicine to escape from teaching and examinations which encourage our students only 'to reproduce the knowledge in the examination'.

CALBERT I. PHILLIPS

Correspondence

The fishmouth phenomenon in retinal detachment

SIR, In his article Mr Colin H. Birchall¹ mentions that Pruett concludes² that the length of a limbus-parallel buckle and the shape of the implant or explant contribute to the pathogenesis of the fishmouth phenomenon. There is, however, an article he did not refer to that predates Pruett's article by 2 years.³ That article

rigorously analyses the geometry of explant buckles and from that analysis concludes that the shape, or more precisely the orientation, of the explant and the length of a limbus parallel buckle explant contribute to the fishmouth phenomenon.

A meridional orientation for a silicone sponge explant is preferred to a limbus-parallel orientation; the wedge-shaped implant proposed by Pruett appears to accomplish the same as the meridional silicone sponge explant. If a sponge explant is placed in a limbus parallel direction, a length less than 90° is unlikely to produce fishmouthing, whereas a length greater than 90° is likely to produce retinal folds on the buckle and the fishmouthing phenomenon. An additional tight encircling band can exacerbate these effects.

MICHAEL GOLDBAUM

Division of Ophthalmology (H-898),
University Hospital,
225 Dickinson Street,
San Diego, California 92103.

References

¹Birchall CH. The fishmouth phenomenon in retinal detachment: old concepts revisited. *Br J Ophthalmol* 1979; **63**: 507-10.

²Pruett RC. The fishmouth phenomenon II. *Arch Ophthalmol* 1977; **95**: 1782-7.

³Goldbaum MH, Smithline M, Poole TA, Lincoff HA. Geometric analysis of radial buckling. *Am J Ophthalmol* 1975; **79**: 958-65.

SIR, I wish to thank Dr Goldbaum for his letter confirming the factors involved in the pathogenesis of the fishmouth phenomenon in retinal detachment surgery. We are in broad agreement.

My phrase 'relative to the circle of the eye that is being indented' qualifies the factor of the length of a limbus parallel buckle. I agree that a length of limbus parallel buckle of less than 90° sector is unlikely in the majority of patients to produce the phenomenon if other contributing factors are absent.

The third factor not mentioned in Dr Goldbaum's letter is the height of the buckle. This is important. Dr Goldbaum draws attention to this in his calculations in his paper¹ and he also mentions in his letter that 'an additional tight encircling band can exacerbate the effect'. Depending on the position of such an additional band this may increase the height of the buckle.

COLIN H. BIRCHALL

Suite 201-1750 East 10th Ave.,
Vancouver V5N 5K4,
British Columbia.

Reference

¹Goldbaum MH, Smithline M, Poole TA, Lincoff HA. Geometric analysis of radial buckling. *Am J Ophthalmol* 1975; **79**: 958-65.

Seasonal incidence of retinal detachment

SIR, The catchment area of the Princess Margaret Hospital, Swindon, is about 250 000 people. Between January 1973 and December 1979 (7 years) 140 patients were operated on for detached retina (all first operations). Twice as many occurred in the first 4 months of the year. There must be, as in any biological series, a monthly detached retina mean, the usual explanation being a combination of anatomical defects and physical stress. Is it possible that there is an additive due to heavy head colds? Maybe not, because November's figures for the period reviewed were the lowest of all despite the fact that 'November's chill blows loud wi' angry sugh'. Whatever the explanation, I always brace myself for a run of detachments after New Year, and it always happens.

Princess Margaret Hospital,
Okus Road,
Swindon SN1 4JU.

F. C. RODGER

Notes

All-India Ophthalmological Conference

The fortieth All-India Ophthalmological Conference will be held at Ravindra Nath Tagore Medical College, Udaipur, on 10-13 January 1981. Further details from Professor M. R. Jain, Ravindra Nath Tagore Medical College, Udaipur, Pin-313001, India.

Glaucoma symposium

The Israel International Symposium on Glaucoma will take place at Tel Aviv, Israel, on 3-5 September 1980. Details from the Secretariat, Israel International Symposium on Glaucoma, PO Box 16271, Tel Aviv, Israel.

Surgical aphakia

The Rochester Eye Institute and the Department of Ophthalmology at Park Ridge Hospital, Rochester, New York, will hold the fifth annual ophthalmic seminar on 15-16 August 1980 at the Rochester Americana Hotel. Details from Ms Katherine Sgabelloni, RN Co-ordinator, Ophthalmic Services, Park Ridge Hospital, 1555 Long Pond Road, Rochester, New York 14626, USA.

American Academy of Ophthalmology

The annual meeting has been rescheduled at Chicago's McCormick Place on 2-7 November 1980. Further details from the American Academy of Ophthalmology, 1833 Fillmore Street, PO Box 7424, San Francisco, CA 94120, USA.

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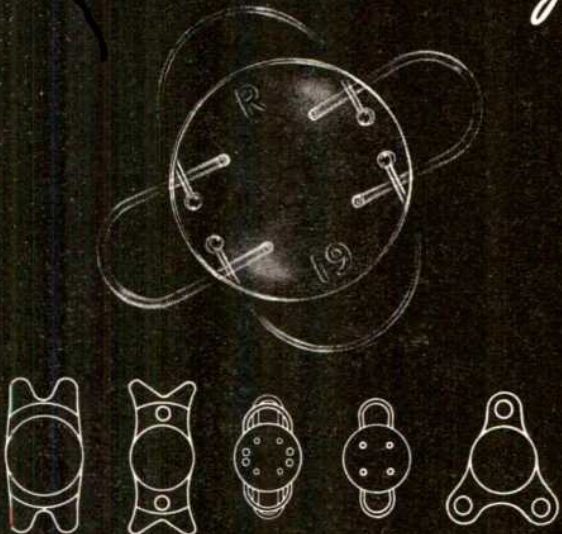
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³Grey EF. Diseases of the pancreas. In: Green AB, Brown CD, eds. *Textbook of Medicine*. London: Silver Books, 1980: 349-62.

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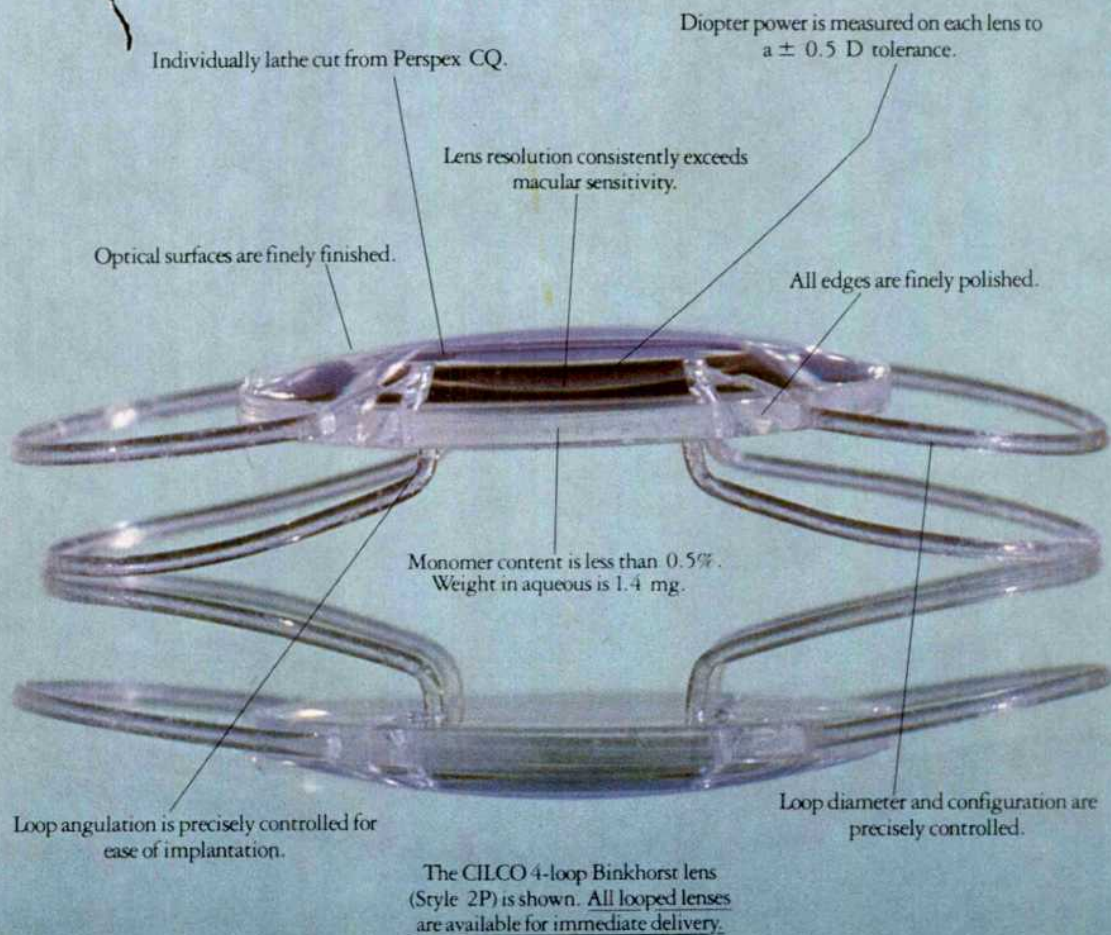
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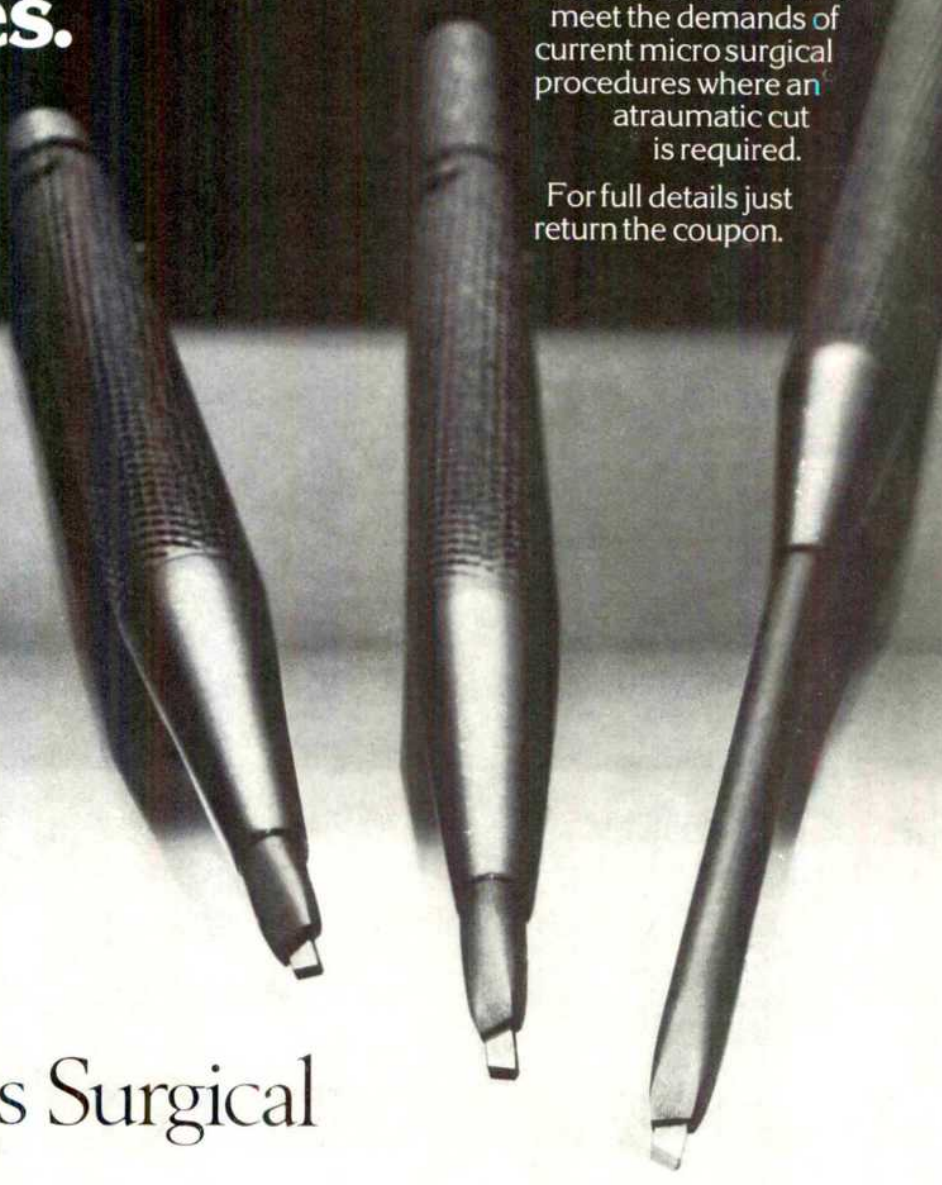
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Reports:

Ocular trauma • Viral Eye diseases

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Anterior Segment Microsurgery • Fundus in metabolic Eye diseases • Parasitic Eye diseases (Onchocercosis, Echinococcosis...) • EMI-scanning in Neuro-Ophthalmology

Round Tables:

Early History of Ophthalmology (Egypt, India, Greece, Arabic World...) • Traditional Medicine (acupuncture, herbal medicine) • Contactology in the diseases of the anterior segment • Trachoma (diagnosis and treatment) • Glaucoma (detection and medical treatment) • Manpower and prevention of blindness

2. TECHNICAL AND DRUGS EXHIBIT

There will be an exhibit of ophthalmological and surgical instruments prosthesis as well as drugs and books related to the eye

3. CULTURAL PROGRAMME

Exhibit of medical manuscripts • Festival of Arts and Archeology • Congress Special stamp issuing • Other cultural and artistic events (exhibit of paintings and lectures)

4. SOCIAL PROGRAMME

Saturday 25: Welcome reception by the Congress Committee

Sunday 26: Dinner offered by the Mayor of Tunis

Monday 27: Concert by the Rachidia Orchestra and dances given by the National Cultural Committee

Wednesday 29: Closure Banquet

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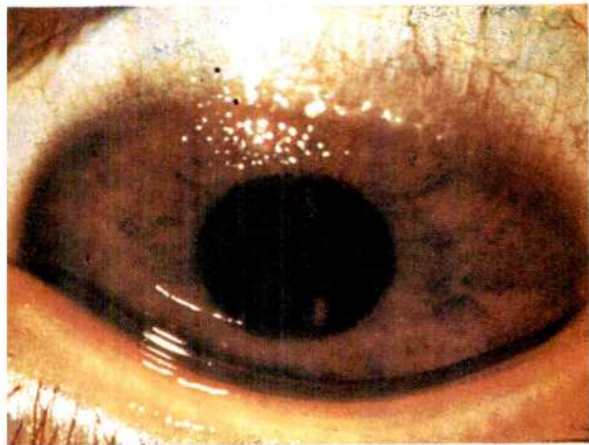
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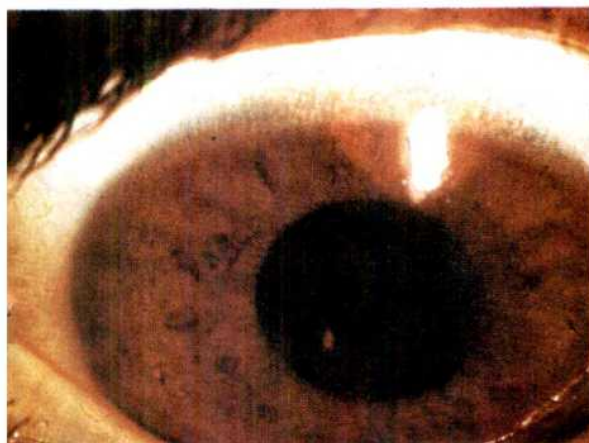
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DOSAGE AND ADMINISTRATION The usual dosage is one drop in affected eye(s) once daily. However the dosage should be adjusted to meet the needs of the individual patient

CONTRA-INDICATIONS, WARNINGS, ETC Should not be used in closed-angle glaucoma, since the dilation of the pupil may precipitate an acute attack. Undesirable side reactions may include eye pain or ache, brow ache, headache, conjunctival hyperaemia and allergic lid reactions. Adrenochrome deposits in the conjunctiva and cornea after prolonged adrenaline therapy have been reported. Adrenaline has been reported to produce macular oedema in some aphakic patients and should be used with caution in these patients

PHARMACEUTICAL PRECAUTIONS Protect from excessive light. If the solution discolours or a precipitate forms it should be discarded
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FURTHER INFORMATION Nil
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Dosage and administration Recommended therapy is one drop 0.25% solution in the affected eye twice a day.

If clinical response is not adequate, dosage may be changed to one drop 0.5% solution in each affected eye twice a day.

If the intra-ocular pressure is maintained at satisfactory levels many patients can then be placed on once-a-day therapy. Because of naturally occurring diurnal variations in intra-ocular pressure, satisfactory response is best determined by measuring the intra-ocular pressure at different times during the day.

Clinical trials have shown the addition of TIMOPTOL to be useful in patients who respond inadequately to maximum antiglaucoma drug therapy.

In the event that further control of intra-ocular pressure is needed, concomitant therapy with miotics, adrenaline, and systemically administered carbonic anhydrase inhibitors may be instituted.

When patients are being transferred from other antiglaucoma agents, on the first day continue with the agent(s) already being used and add one drop of 0.25% TIMOPTOL in the eye twice a day. On the following day, discontinue the previously used antiglaucoma agent(s) completely and continue with TIMOPTOL. If a higher dosage of TIMOPTOL is required, substitute one drop of 0.5% solution in the eye twice a day.

When TIMOPTOL is to be added to other antiglaucoma therapy, administer one drop of 0.25% TIMOPTOL in the eye twice a day. If a higher dosage of TIMOPTOL is required substitute one drop of 0.5% solution in the eye twice a day.

Contra-indication Hypersensitivity to Ophthalmic Solution TIMOPTOL.

Precautions Ophthalmic Solution TIMOPTOL should be used with caution in patients with known contra-indications to systemic use of beta-adrenergic receptor blocking agents such as patients with bronchospastic disease and congestive heart failure.

There have been reports of skin rashes and/or dry eyes associated with the use of systemically administered beta-adrenergic receptor blocking drugs.

The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving the beta-blockade should be gradual.

Although TIMOPTOL has been used in a small number of patients wearing contact lenses made of polymethylmethacrylate (PMMA), and there have been no reports of adverse effects, at present, experience is too limited to enable a conclusion on safety to be made.

Use in pregnancy TIMOPTOL has not been studied in human pregnancy. The use of Ophthalmic Solution TIMOPTOL requires that the anticipated benefit be weighed against possible hazards.

Use in children Since clinical studies in children have not been conducted, TIMOPTOL is not currently recommended for use in children.

Side effects Ophthalmic Solution TIMOPTOL is usually well tolerated. Occasionally signs and symptoms of mild ocular irritation have been reported. Local hypersensitivity reactions have occurred rarely.

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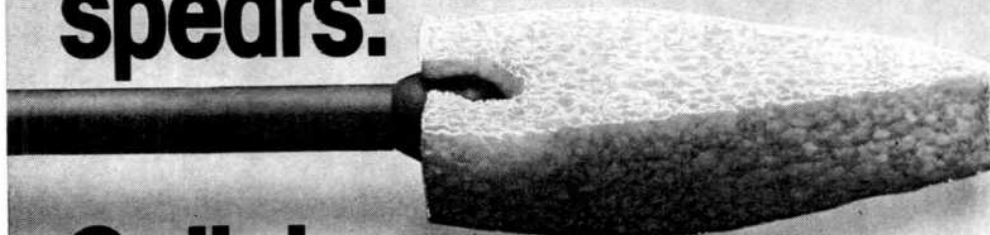
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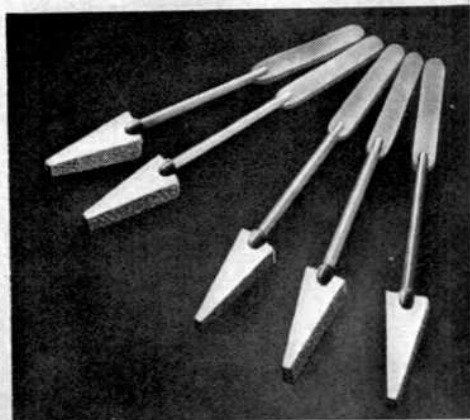


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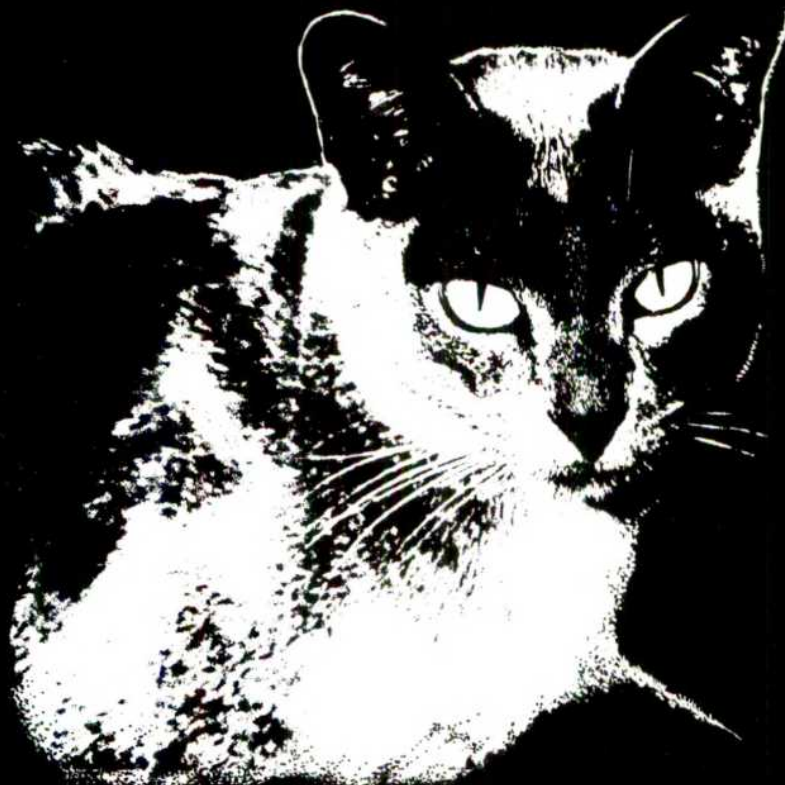
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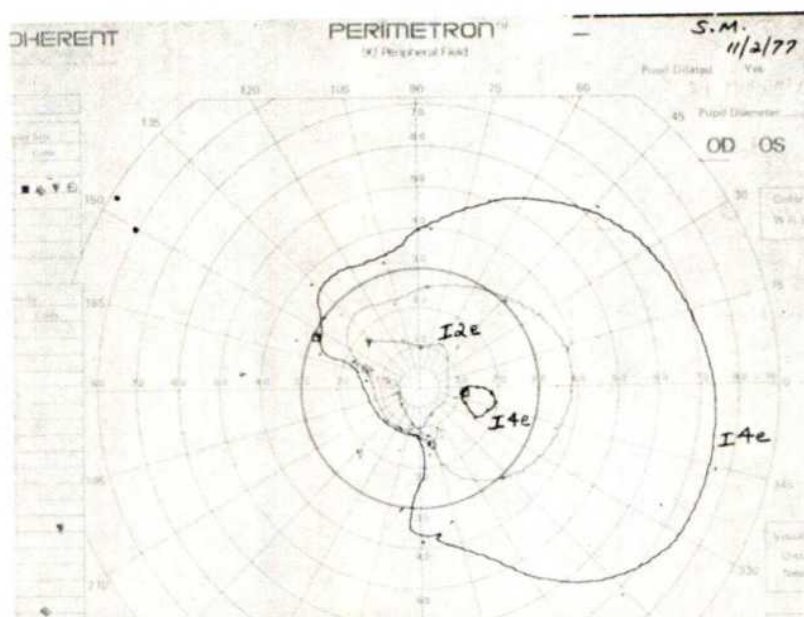
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Xenon arc photocoagulation for the treatment of diabetic maculopathy

Interim report of a multicentre controlled clinical study

C. TOWNSEND,¹ J. BAILEY,² AND E. KOHNER¹

From the ¹Hammersmith Hospital, London, and the ²London School of Hygiene and Tropical Medicine

SUMMARY The results of a randomised controlled clinical study in the treatment of diabetic maculopathy are reported. Ninety-nine patients with two similarly affected eyes had one—chosen by random procedure—treated, while the other was left as an untreated control. Visual acuity was maintained in the treated eyes, while it deteriorated in the untreated eyes, reaching over 2 lines difference after 4 years. The difference in deterioration was significantly less in treated than in untreated eyes at each assessment. After 4 years the difference between the 2 eyes was greatest in those with initially good vision. There was no difference in visual acuity in patients whose initial vision was less than 6/36. Only 9 treated but 25 control eyes lost vision to blindness ($P < 0.001$). It is concluded that maculopathy is a treatable form of diabetic retinopathy if treated before severe visual loss occurs.

In diabetic retinopathy loss of visual acuity can result either from the sequelae of proliferative retinopathy or from maculopathy. During the last few years reports have been published showing the effectiveness of photocoagulation for proliferative retinopathy, especially when the optic disc is involved.¹⁻⁴ There is much less evidence about the efficacy of treatment in diabetic maculopathy. There are only 3 previous reports on randomised controlled studies of diabetic maculopathy.⁵⁻⁷ None of these followed up the patients for longer than 3 years. In our present paper we are reporting the results of treatment for diabetic maculopathy with xenon arc photocoagulation in the British Multicentre Study at a time when an important number of patients have been followed up for 5 years.

Statisticians: Professor P. Armitage and Miss Judith M. Bailey. Medical advisers: Professor H. Keen and Dr E. M. Kohner. Participating ophthalmologists: R. K. Blach (Hammersmith/Moorfields, London), A. M. Hamilton (Hammersmith/Moorfields, London), M. Odland (Bergen), H. Cheng (Tunbridge Wells), J. Richardson (Newcastle), J. Shilling (St Thomas's Hospital, London), K. Rubenstein (Birmingham), N. R. Galloway (Nottingham). Mr Townsend was British Diabetic Association Co-ordinator of Study.

Correspondence to Dr Eva M. Kohner, Department of Medicine, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS.

Patients and methods

These were described in detail in 1975.⁷ A summary is given below.

DEFINITIONS

Macula was defined as the fovea and the area immediately surrounding it extending to approximately 1 disc diameter from the centre of the fovea in all directions.

Maculopathy was defined as a visual acuity of 6/9 or less on the Snellen test type in the presence of macular oedema in association with haemorrhages, microaneurysms, and exudates. Patients with a visual acuity better than 6/9 were included if ophthalmoscopically hard exudates were seen to encroach on the macula.

PATIENTS

Patients were included in the trial if they had diabetic maculopathy of a similar severity in both eyes. Similarity was defined as a visual acuity within 2 lines of the Snellen test type between the 2 eyes and clinically observable features of retinopathy of approximately the same severity (within 2 Hammersmith Hospital Grades).⁸

Patients were excluded from the trial if: (1) They

were unlikely to survive for 1 year; (2) there was intercurrent disease of the eyes or visual pathways likely to affect visual acuity or clarity of the media during the period of observation; (3) there was more than a wisp of fibrous retinitis proliferans in the fundus; (4) there was macular scarring; (5) there was detachment or retinoschisis in the temporal half of the fundus; (6) the media were not clear enough for fundus photography and unimpeded central vision.

The presence of early new vessels did not automatically exclude a patient from the trial, but new vessels if present had to be present in both eyes for the patient to be included. This combination of proliferative retinopathy and maculopathy was seen in 13 out of 99 patients.

METHODS

Randomisation. Patients whose eyes were suitable for the trial were entered after obtaining informed consent. One eye chosen by random procedure was allocated for treatment while the other remained untreated. Randomisation was carried out by the co-ordinating centre. Each treating centre was provided with sealed envelopes containing the randomisation; the envelopes were numbered and opened in strict numerical order.

Treatment. The eye chosen for treatment had xenon arc photocoagulation, usually under local (retrobulbar) anaesthesia but occasionally under general anaesthesia. The apparatus used was the Zeiss (Oberkochen) or the O'Malley Log 2 Light Coagulator. Treatment was given according to the clinical judgment of the ophthalmologist in charge. The treated eye could be treated any number of times. Neither the number, the site, the intensity of, nor the area covered by the burns used was specified. Once an eye had been selected for treatment the mode and number of treatments was left to the discretion of the ophthalmologist no matter what lesion, whether new vessel or maculopathy. In general the treatment given was focal to areas of microvascular abnormalities between the superior and inferior temporal vessels, including the area lateral to the macula. Focal treatment was also used initially for new vessels when present. Pan-retinal photocoagulation for proliferative lesions was carried out if patients developed new vessels on the optic disc in the treated eye. There were 9 such eyes. Control eyes were never treated unless new vessels developed on the optic disc; in that case the patient was withdrawn from the trial.

Data collected. The corrected visual acuity was recorded at the beginning and at yearly intervals thereafter. When possible the person testing was not involved in the treatment. This was achieved in

at least 80 of the patients. At each annual assessment the disc and macula were photographed and were graded by the secretary and co-ordinator using the Hammersmith Hospital Grading System.⁸ Details of the patients' general health, their management by the physicians, and their diabetic control were also recorded.

This paper reports only changes in the visual acuity. A full analysis of other features, including mortality and medical data, will appear in the final report of this trial. Only patients followed up for at least 1 year are included in this study.

ANALYSIS

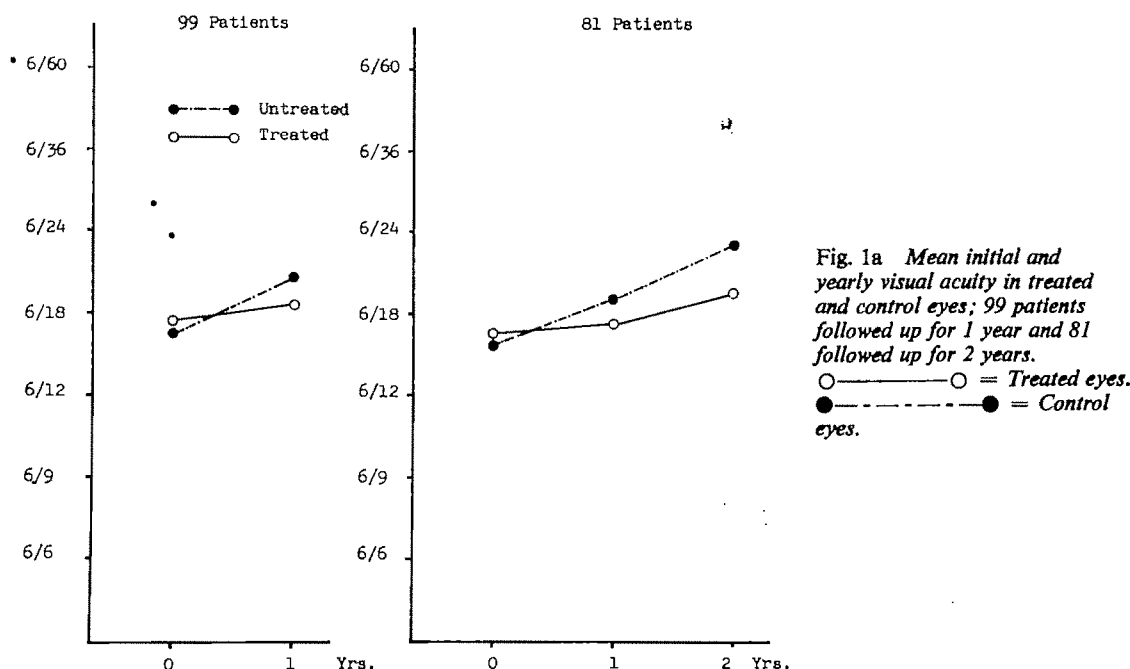
The data were analysed on the CDC 6600 computer at the University of London Computer Centre. For the purpose of the analysis the visual acuities were coded from 1 to 10 (1 for 6/6, 2 for 6/9, etc.). An eye was considered to be worse if the visual acuity worsened by 1 line or more on the Snellen chart. Similarly, an eye was considered to have improved if the visual acuity improved by 1 line or more.

Two tests were done for each yearly follow-up to compare the behaviour of the treated and untreated eyes. Firstly, for each patient the deterioration (measured by number of lines) in each eye since the initial assessment was calculated, and a paired *t* test was performed on these changes. For example, at the 1-year follow-up the difference in deterioration of vision between treated and untreated eye, *d*, was calculated as $(AV_{ui} - AV_{uo}) - (VA_{ti} - VA_{to})$ where *VA* = visual acuity and *u* and *t* stand for untreated and treated eyes; *i* and *o* stand for initial and one year values. Secondly, McNemar's test was used to compare those in whom only the treated eye was worse with the patients in whom only the untreated eye was worse. Another test was done on those patients who were blind at the last 2 annual assessments. For these patients McNemar's test was again used to compare the number of patients who were blind only in the treated eye with those who were blind only in the untreated eye.

The mean visual acuity for treated eyes and untreated eyes was also calculated for each assessment. Plots were also made of initial visual acuity against annual visual acuity.

Results

A total of 99 patients were followed up for at least 1 year. Of these, 81 were followed up for at least 2 years, 71 for at least 3 years, 35 for at least 4 years, and 23 for 5 years. The mean age of entry to the trial was 58.4 years (range 20–76). Known duration of diabetes was 8.8 years (range 0–34).



VISUAL ACUITIES

Fig. 1 (a-c) shows the mean yearly visual acuities for the patients followed up for 1 to 5 years. This figure shows that initially, and at 1 year, the visual acuities of the treated and untreated eyes were similar. At 2 years the difference in visual acuity was half a line in favour of treatment. At 3 years the difference increased to almost 1 line and at 4 and 5 years to 2 lines in favour of treatment. When all eyes were considered, the vision of the treated eyes deteriorated significantly less than the vision of the untreated eyes at each yearly interval (Table 1). In the group with mean visual acuities of 6/12, 6/18,

and 6/24 the difference in deterioration in visual acuity was less in the treated eyes than the untreated ones, reaching significant levels for the first 4 years (Table 2). The results for the fifth assessment may be significant when a greater number have reached this stage. There were only 19 patients with an initial visual acuity of 6/9 or better, and only 6 of these have been followed up for the full 5 years. It is in this group that the greatest difference in deterioration was seen, amounting to over 4 lines difference at 4 and 5 years in favour of treatment (Table 3). In the 19 patients with an initial visual acuity of 6/36 or worse there was at no time a

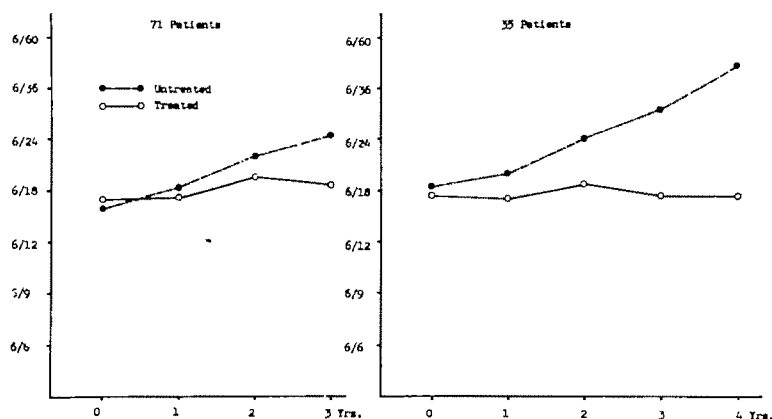
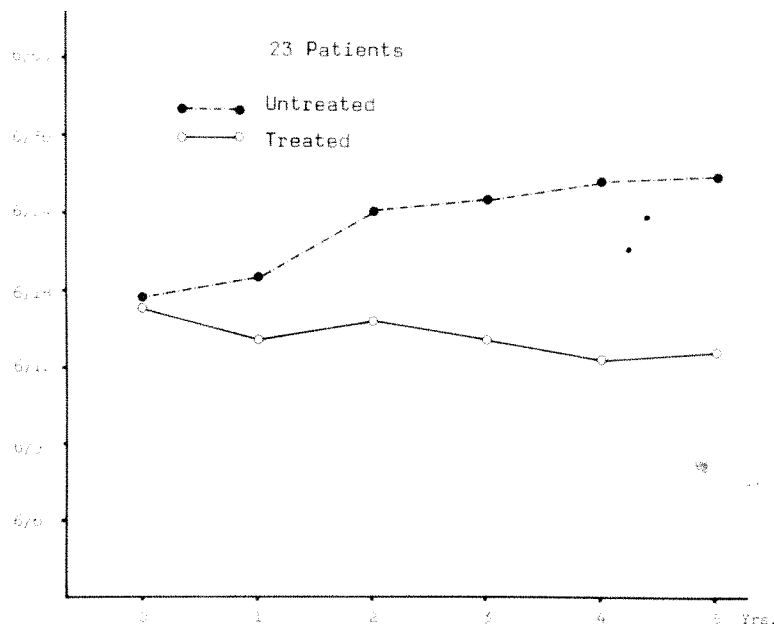


Fig. 1b Same as Fig. 1a, but for 71 patients followed up for 3 years and 58 patients followed up for 4 years.

Fig. 1c Same as Fig. 1a, but for 23 patients followed up for 5 years.



statistical significance in difference in deterioration between the treated and the untreated eyes.

After 2 years there were 20 patients for whom the untreated eye was worse when the treated eye improved or remained unchanged, but only 6 patients for whom only the treated eye was worse (Table 4). McNemar's test gave $\chi^2=6.5$ ($P<0.05$). Similar results were obtained after 3 years ($P<0.001$), 4 years ($P<0.01$), and 5 years ($P<0.01$).

Table 1 Difference in deterioration of vision all patients

Time (yr)	N	d	SE(d)	t	P
1	99	0.535	0.180	3.0	<0.01
2	81	0.667	0.211	3.2	<0.01
3	71	1.042	0.297	3.5	<0.001
4	35	2.000	0.458	4.4	<0.001
5	23	2.130	0.570	3.7	<0.01

N = number of patients. d = Difference in deterioration of vision between treated and untreated eyes. SE = standard error.

Table 2 Difference in deterioration of vision patients with mean initial vision 6/12-6/24

Time (yr)	N	d	SE(d)	t	P
1	61	0.689	0.226	3.0	<0.01
2	49	0.694	0.248	2.8	<0.01
3	44	1.273	0.376	3.4	<0.01
4	21	1.762	0.585	3.0	<0.01
5	13	1.385	0.646	2.1	NS

Annotation as in Table 1.

Table 3 Difference in deterioration of vision mean initial vision 6/6-6/9

Time (yr)	N	d	SE(d)	t	P
1	19	0.211	0.430	0.5	NS
2	18	1.056	0.618	1.7	NS
3	15	1.267	0.790	1.6	NS
4	7	4.286	1.017	4.2	<0.01
5	6	4.167	1.352	3.1	<0.01

Annotation as in Table 1.

Table 4 Changes of visual acuity (Snellen)

Follow-up	Treated eye	Untreated eye Improved/same	Worse	Total
After 1 yr	Improved/same Worse Total	45 9 54	20 25 45	65 34 99
After 2 yr	Improved/same Worse Total	29 6 35	20 26 46	49 32 81
After 3 yr	Improved/same Worse Total	27 3 30	20 21 41	47 24 71
After 4 yr	Improved/same Worse Total	13 0 13	11 11 22	24 11 35
After 5 yr	Improved/same Worse Total	8 0 8	10 5 15	18 5 23

After 1 year: In 45 patients both treated and untreated eyes improved or remained the same. In 20 patients the untreated eye deteriorated, while the treated eye improved or remained the same. In 9 patients the treated eye worsened but the untreated eye improved or remained the same. In 25 patients both eyes became worse. Each year is set out similarly.

A graphical representation of the change in visual acuity of each individual eye was made by plotting the visual acuity from each annual assessment against the initial vision. Figs. 2 and 3 are such plots at 4 and 5 years respectively when the

changes were largest. Both these figures illustrate that considerably fewer of the treated eyes deteriorated than did the untreated eyes, and this is particularly noticeable in eyes with initially good visual acuity of 6/6-6/12.

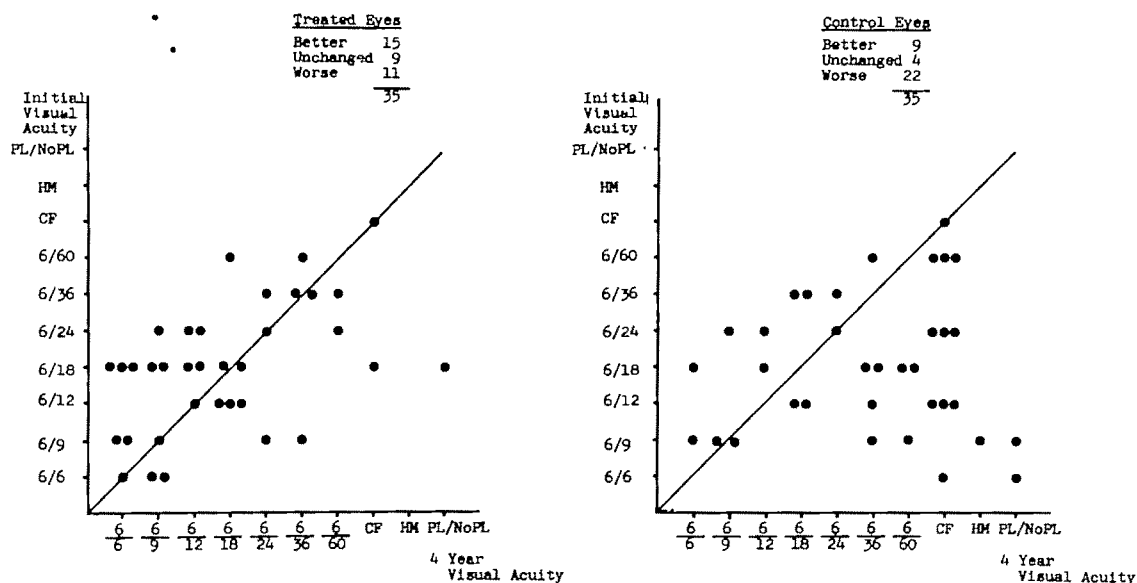


Fig. 2 Initial and 4-year visual acuity of 35 patients followed up for this time. Each eye is represented by a dot. Diagonal line represents no change. CF = count fingers. HM = hand movements. PL = perception of light. NPL = no perception of light.

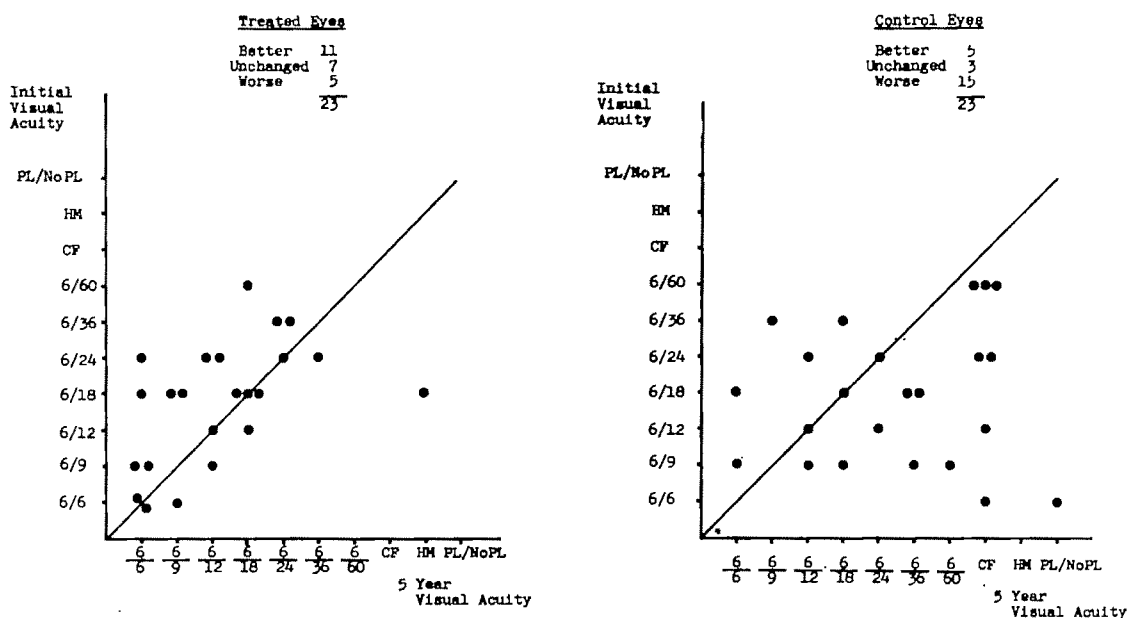


Fig. 3 Initial and 5-year visual acuity in 23 patients followed up for 5 years. Annotation as in Fig. 2.

Table 5 *Causes of visual loss*

	<i>Treated</i>	<i>Untreated</i>
Hard exudate plaque and scar	3	12
Gross macular oedema	3	8
Complications of new vessels	3	5
Total	9	25

BLINDNESS

In this study blindness was defined as a visual acuity of 6/60 or worse for 2 consecutive yearly assessments including the latest one. Of 81 patients followed up for at least 2 years the following were blind for the last two assessments: 7 in both eyes, 2 in the treated eye only, and 18 in the untreated eye only ($P < 0.001$ for McNemar's test). A further 3 treated and 3 untreated eyes were blind at 1 stage but improved to 6/36 or better by the latest assessment, and are therefore not included among the blind.

The causes of visual loss are summarised in Table 5. The initial causes of visual loss were mostly the development of hard exudate plaque in the fovea, or worsening of macular oedema. This occurred in 6 treated eyes and 20 untreated eyes. In 1 treated eye the extension of the hard exudate into the fovea occurred after the first 3 days following treatment and was therefore attributed to the treatment. New vessels and their complications, vitreous haemorrhage, fibrous tissue formation, and thrombotic glaucoma were the primary cause of visual loss in 5 untreated and 3 treated eyes. Three of the untreated eyes which became blind had new vessels present in the affected eye at the time of entry into the study. Vitreous haemorrhage caused severe visual loss (worse than 6/60) as a secondary cause in 6 untreated and 3 treated eyes. These eyes were already blind from maculopathy but retained navigational vision until the development of the haemorrhage. In 1 treated eye vitreous haemorrhage occurred after cataract extraction, and in another eye new vessels were not seen on any previous examination, probably because of lens opacities. Of the blind eyes 3 treated and 6 untreated eyes were already 6/60 at the initial assessment. Five treated eyes which had a visual acuity of 6/60 at entry into the study improved slightly during the follow-up, but none of the untreated eyes with such poor initial visual acuities showed improvement.

Discussion

This study confirms previous results^{6,7} that diabetic maculopathy benefits from treatment with xenon arc photocoagulation. There are, however, some

important differences between the results reported here and those reported in 1975.⁷ In the previous report, while the initial visual acuity was similar in the treated and untreated eyes, at 1, 2, and 3 years the treated eyes had 1 line less deterioration of vision than the untreated eyes. This difference seemed to be constant, suggesting that photocoagulation delays but does not prevent deterioration of vision in this condition. The present report, which includes more patients followed up for a longer period of time, leads us to a different conclusion. Instead of the eyes deteriorating in parallel, with the treated eye having significantly better visual acuity than the untreated, we see that there is divergence increasing over the third, fourth, and fifth years. The treated eyes maintain their visual acuities, but those of the untreated group deteriorate.

That the divergence takes time to appear can be explained by several factors. In the absence of treatment macular oedema increases, but slowly, requiring 3 or more years to show its full effect. While the deposition of hard exudate in the fovea may reduce the visual acuity there is a delay period before the exudate is actually deposited in the small central area where it causes most harm to the vision.

The development of reduced capillary perfusion is slow. It may involve the macular arcade with loss of central vision. The process may be altered by photocoagulation. It has been shown in the normal cat retina that photocoagulation alters retinal blood flow and its distribution.⁹ It would be interesting to measure blood flow in human capillary beds. That would show whether photocoagulation redistributes flow in such a way that central areas, such as the macula, may have their blood supply enhanced.

Finally, some patients lose vision from complications of new vessel formation. These take several years before visual loss becomes apparent.

The results of treatment are not as marked as for new vessels. A cause of the limited divergence is that irreversible damage to foveal receptors may have occurred even in the treated eye before entry into the trial; once foveal receptors are destroyed by exudate or oedema they cannot regenerate. If these morphological changes were reversible, there would be an earlier more marked divergence in visual acuity, brought about by an improvement in function in treated eyes with resolution of the oedema or exudate.

A further cause of lack of dramatic change in vision is that treatment itself is associated with a degree of morbidity with some visual deterioration which, though it usually improves, does not do so completely.

In the previous paper² patients with initial visual

acuity of 6/6 and 6/9 were reported not to have benefited from treatment. In the small number followed up here, again there was no significant treatment benefit obtained up to 3 years, but after that time the difference in deterioration was over 4 lines of visual acuity in favour of treatment. These results are striking and indicate that early treatment of maculopathy, such as that associated with circinate exudates, may prevent visual loss in these patients at a later stage. The ideal time of treatment is therefore before any marked visual loss has occurred. However, in spite of these results caution in decision of early treatment may be indicated, especially if there is no previous recorded visual deterioration. The number of patients in this group is small. Perhaps we should not therefore be hasty in drawing very firm conclusions from this result, though it was statistically highly significant, especially as treatment does carry a risk of morbidity. Extension of hard exudates in the immediate post-treatment period is common, presumably because of transient increase in leakage. If the hard exudates are near the fovea, they may extend into it, causing profound visual loss.

This study, like the previous one by Patz *et al.*⁵ and the earlier report on the same patients⁷ confirms that poor initial visual acuity precludes good response to photocoagulation.

The reduction of blindness in the treated eyes is similar to that reported earlier. It must be emphasised, as it was previously, that new vessels and their complications were an important primary and secondary cause of visual loss in these patients. It could be argued that in the treated group this could have been prevented by initial extensive pattern bombing (scatter treatment) of the retinal periphery. However, because in maculopathy there is a loss of central vision, the aim was to preserve peripheral field, and scatter treatment was not given routinely. At the time of starting this study the natural history of new vessels was not clearly established, and this is why patients with early new vessels were included in the maculopathy study. However, the major cause of visual loss in both treated and untreated eyes was progression of the maculopathy. The difference in deterioration therefore cannot be ascribed to the treatment of proliferative retinopathy. The results, however, emphasise the importance of regular follow-up of patients with diabetic maculopathy, including careful examination of the disc and peripheral retina. Careful examination is important, because in this group of elderly patients frequent lens and vitreous opacities make detection of early new vessels difficult. Indeed, they were never diagnosed prior to the vitreous haemorrhage in some of the patients.

During the period of this study we have become aware of the fact that maculopathy is not a single entity but comprises a variety of subgroups which are differentiated by the relationship of hard exudates and haemorrhages, ischaemia, and oedema. These features determine not only the initial visual acuity but also response to treatment. Subdivision into these subgroup depends on analysis of colour photographs and fluorescein angiograms and is in process.

The results reported in this paper were achieved with the xenon arc photocoagulator. The argon laser will probably be more rather than less effective in the treatment of maculopathy because of its smaller spot size. A randomised study using the laser is now starting in the USA. In the meantime it is suggested, as the result of the findings reported in this paper, that photocoagulation is an effective way of treating diabetic maculopathy and maintaining vision provided the initial acuity is better than 6/36.

We thank all the research fellows who helped with the study during the follow-up period and without whom we could not have managed the work. In particular we are grateful to Dr Margaret Kearns, who was looking after the largest group of patients almost single-handed for 6 months. We also wish to thank Miss S. Suen, who did all the computing work and drew the graphs. The illustrations were prepared by Mr K. Sehmi and manuscripts typed by Mrs R. Hodgetts and Miss C. Giffen.

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Organised macular plaques in exudative diabetic maculopathy

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SUMMARY Plaques of hard exudate measuring 0.5 to 1.0 disc diameters, which occurred in 5 eyes of 4 patients with diabetic maculopathy, showed complete organisation in 8 to 18 months with the formation of scars measuring 0.2 to 0.5 disc diameters. The visual acuity was related to the size and situation of the scar within the fovea, and, when the foveola was involved by plaque formation, visual reduction did not progress with subsequent formation of scar tissue. Fluorescein angiograms showed absence of ingrowing choroidal neovascularisation and a discrete residual hyperfluorescence beneath the resolving plaques and within the scar tissue, which resembled a serous detachment of pigment epithelium but may have resulted from a combination of pigment atrophy and leakage from retinal capillaries. This late clinical appearance may be the only ophthalmoscopic evidence that a severe exudative maculopathy has been primarily responsible for severe visual loss, and should be differentiated from cicatricial disciform lesions in older patients. The absence of ingrowing choroidal neovascularisation, subretinal haemorrhage, and pronounced serous retinal detachment substantiates our previous conclusions based on a morphological study from a limited number of sections that the origin of the fibrous replacement was not choroidal but was derived partly from the pigment epithelium and partly from the retinal vasculature. Juxtaposition of a deeply situated hard exudate plaque and the retinal pigment epithelium may initiate focal metaplasia and subsequent organisation with scar formation.

Spontaneous progression and regression of hard exudate in diabetic maculopathy was described by King *et al.*¹ and Dobree,² who found that plaque formation required years for resolution and was not followed by visual recovery. In a previous report³ we described the pathology of an organised macular plaque in exudative diabetic maculopathy and observed that the fibrous replacement was partly retinovascular and partly pigment epithelial in origin, suggesting that it was a specific pathological entity. The present study reports the resolution of macular plaques accompanied by organisation in 5 eyes of 4 patients with diabetic maculopathy. This late clinical appearance, which is fully described for the first time, may be the only ophthalmoscopic evidence that a severe exudative maculopathy has been primarily responsible for severe visual loss, and should be differentiated from disciform macular degeneration in older patients.

Material and methods

The cases were obtained by reviewing the biomicroscopic descriptions and stereo colour photographs of patients showing exudative diabetic maculopathy with plaques measuring $\frac{1}{2}$ of a disc diameter or greater, who had attended the Diabetic Retinopathy Service during the past 6 years. Only those patients showing the complete evolution from plaque to scar formation have been included in this study. The histological subdivision of macular areas⁴ has been used in the clinical descriptions.

CASE REPORTS

Case 1. A white woman age 57 was diagnosed as diabetic in June 1974 when a mild background retinopathy was discovered. The visual acuity was 6/6 in both eyes. Diabetes was subsequently well controlled on oral medication. There was no hypertension. In February 1975 she complained of fluctuating vision and micropsia in the right eye which had been present for 1 month. The corrected vision was 6/7.5, and there was a plaque of hard

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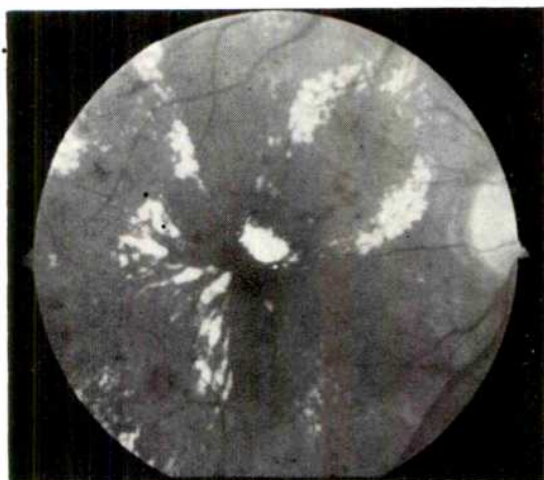


Fig. 1 Case 1, February 1975. Circinate hard exudates and plaque bordering the foveola.

exudate measuring 0.75 disc diameter (DD) bordering the foveola (Fig. 1). Fluorescein angiography showed clusters of microaneurysms, absence of large areas of capillary obliteration, and prominent cystoid retinal oedema within the circinate hard exudate formations. Laser photocoagulation was applied to leaking capillaries in April, May, and August 1975. In July a pigment disturbance was visible within the resolving plaque, and a late angiogram showed a residual hyperfluorescence within the plaque and slight diffuse leakage in the surrounding retina. By October the plaque had

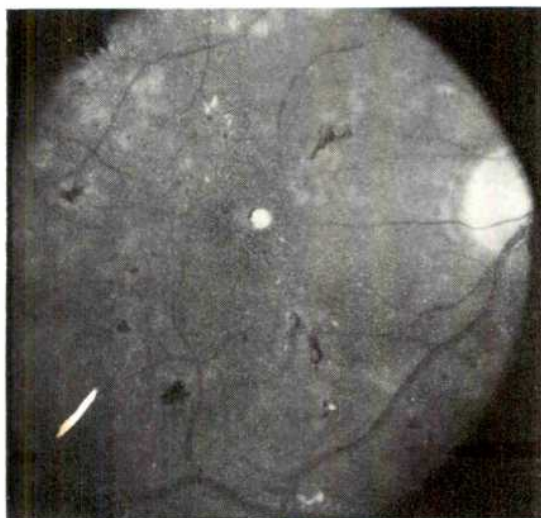


Fig. 2 Case 1, February 1976. Final appearance of the scar.

completely resolved, revealing an elevated grey scar at the margin of the foveola, measuring 0.15 DD, and in February 1976 a strand of glial tissue appeared on the surface (Fig. 2). At the last examination, in September 1978, the visual acuity was 6/6, the scar was unaltered, and there was almost complete resolution of hard exudate throughout the macula. Angiography showed an early hyperfluorescence, slight retinal capillary leakage, and late intense discrete leakage and staining within the scar (Fig. 3). A static visual field examination showed markedly reduced retinal sensitivity in this location.

Case 2. A 34-year-old insulin-dependent male diabetic of 12 years' duration was first examined in June 1969 when he complained of bilateral visual

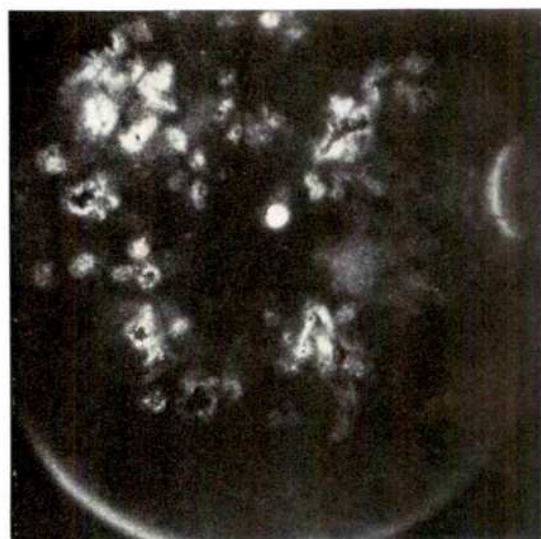


Fig. 3 Case 1, September 1978. Late angiogram shows intense discrete hyperfluorescence and staining within the scar as compared with the control photograph which showed no pseudofluorescence.

deterioration. The blood pressure was normal. The corrected vision was reduced to 6/21 in the right eye and 6/15 in the left eye as a result of a severe exudative diabetic maculopathy. A plaque of hard exudate, 0.75 DD, covered the right foveola (Fig. 4). Fluorescein angiography showed a coarse network of dilated tortuous capillaries, numerous diffusely scattered microaneurysms, widespread leakage and cystoid macular oedema. Within a few months vision deteriorated to 6/120 in the right eye and 6/60 in the left eye. He was treated with clofibrate for 1 year. In July 1970 the plaque had cleared in the right eye revealing an underlying elevated pigmentation (Fig. 5). Retinal neovascularisation

overlying the temporal raphe and elsewhere in the right eye was treated by xenon photocoagulation in February 1971. In July 1973 there was a discrete white scar 0.2 DD, with surrounding pigmentation at the right fovea (Fig. 6). Angiography showed an early hyperfluorescence, retinal capillary leakage (Fig. 7), and late comparatively discrete leakage and staining with the scar (Fig. 8). At the last examination, in October 1975, the corrected vision was 6/15 in the right eye and the macular appearance was unchanged. The patient developed an unexplained jaundice and died in October 1975.

Case 3. A 64-year-old white female diabetic patient, controlled on oral medication for 10 years, experienced a gradual visual deterioration in

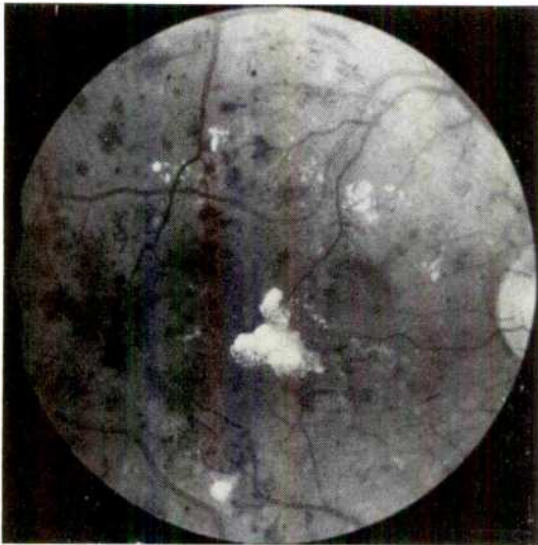


Fig. 4 Case 2, right eye, June 1969. Fundus photograph shows plaque of hard exudate covering the foveola.

her left eye over a 5-month period. She was receiving antihypertensive medication. In March 1974 the corrected vision was 6/6 in the right eye and counting fingers at 1 metre in the left eye. There was a mild background diabetic retinopathy in the right eye, and in the left eye there were circinate formations of hard exudate and a plaque measuring 0.5 DD in the superotemporal fovea, which covered the foveola. Fluorescein angiography showed a marked diffuse capillary leakage, cystoid macular oedema, and late faint hyperfluorescence within the temporal half of the plaque. When she was next examined in September 1974 some circinate hard exudates remained, but the plaque in the left eye had cleared, revealing an elevated pigmented scar, measuring

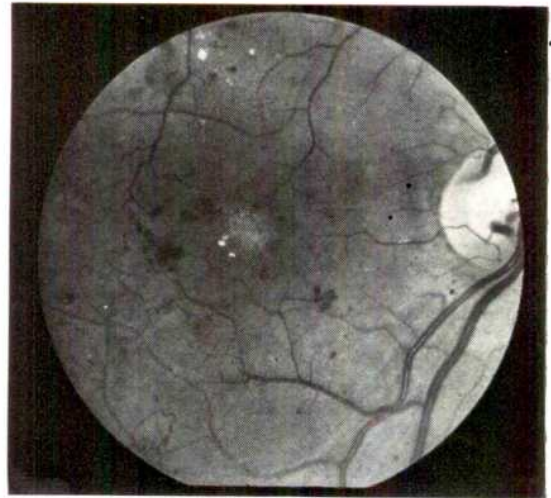


Fig. 5 Case 2, right eye, July 1970. Fundus photograph shows complete resolution of the plaque, revealing underlying elevated pigmentation.

0.25 DD. The visual acuity was 6/120. Another smaller plaque of hard exudate appeared just nasal to the scar in October 1975. Fluorescein angiography showed an early hyperfluorescence within and surrounding the scar and late discrete hyperfluorescence within the scar. In addition there was marked capillary dilatation with numerous microaneurysms throughout the parafoveal capillary plexus, disruption of the inner border, and pronounced diffuse late leakage from retinal capillaries. The visual

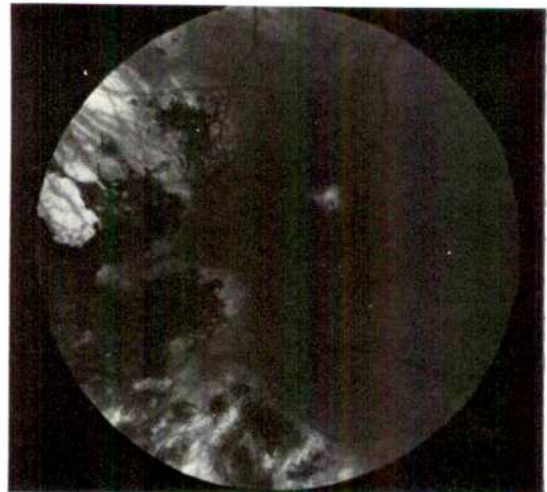


Fig. 6 Case 2, right eye, July 1973. Fundus photograph shows a discrete white scar bordered by pigmentation, and xenon photocoagulation scars temporally.

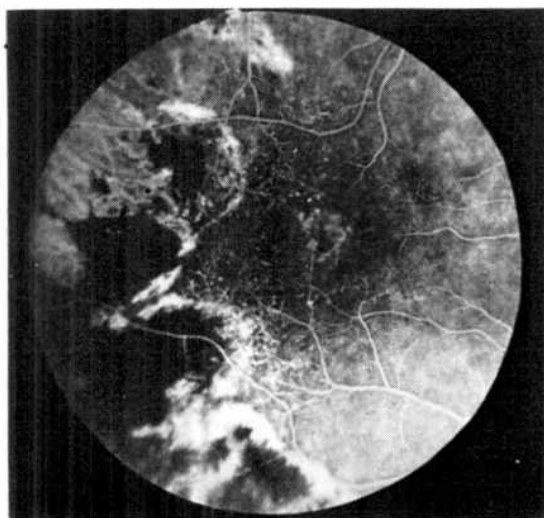


Fig. 7 Case 2, right eye, July 1973. Fluorescein angiogram shows early hyperfluorescence within the scar and diffuse diabetic retinal capillary disease.

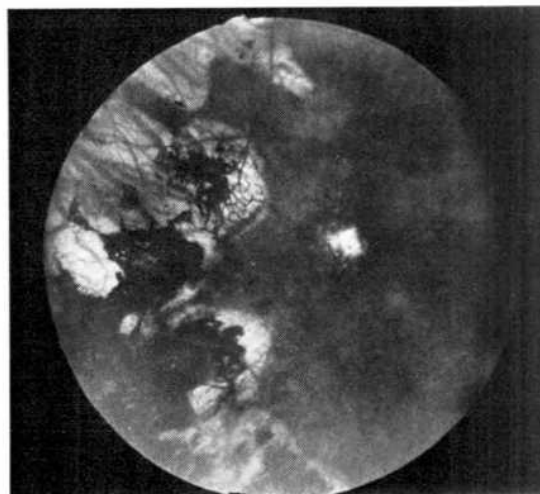


Fig. 8 Case 2, right eye, July 1973. Late angiogram showing residual discrete leakage and staining, as compared to the control photograph, which showed slight pseudofluorescence.

acuity and appearance of the scar was unchanged when last examined in June 1976.

Case 4. A 71-year-old white female, who had been diabetic on insulin for at least 13 years, was examined in January 1975 when she complained of a gradual visual deterioration in both eyes of 1 year's duration. The left eye had deteriorated more rapidly in the preceding month. The blood pressure was normal. The corrected vision was 6/18 in the right eye and 6/30 in the left eye, as the result of a severe exudative diabetic retinopathy with many clusters of hard exudate and cystoid macular oedema. Within a month vision deteriorated to 6/24 in the right eye and 6/90 in the left eye, and in view of the recent rapid deterioration laser photocoagulation was applied to leaking capillaries in both maculae. In April the vision was 6/120 in the right eye and 6/60 in the left eye, and there were sheets of hard exudate throughout both maculae. A hard exudate plaque at the fovea, in both eyes, was observed in September 1975. In March 1976 the plaque measured 0.5 DD in the right eye and 1 DD in the left eye. One year later there was considerable resolution of hard exudate in the right eye and the plaque had resolved, revealing a discrete elevated pigmented scar, 0.3 DD in size, with overlying strands of glial tissue. In the left eye large clusters of hard exudate remained within the macula, but the foveal plaque had resolved and was replaced by a discrete elevated pigmented scar measuring 0.75 DD with overlying preretinal gliosis. At the last examination, in March 1978, both eyes showed an elevated grey scar with

an annulus of pigmentation and slight pigment atrophy, radiating retinal folds, and overlying strands of glial tissue. Angiography showed an early hyperfluorescence and late intense discrete hyperfluorescence within both scars. Throughout both maculae there were multiple areas of capillary obliteration, leaving a coarse network of dilated tortuous capillaries with numerous microaneurysms which showed pronounced late leakage.

Discussion

Foveal scars developed in 5 eyes of 4 patients who showed typical severe exudative diabetic maculopathy with large waxy hard exudate plaques involving the fovea. The appearance most closely resembled the discrete fibrovascular macular scar described in Coats's disease^{5,6} and the cicatricial disciform lesion caused primarily by diseases of the choroid.⁵ The scars were round, discrete, slightly elevated, white or grey in colour, and some showed overlying pigment clumps or a thin annulus of pigment surrounded by slight pigment epithelial atrophy. A thin strand of glial tissue projected forward from the surface of the scar in 4 eyes, and 2 of them also showed radiating retinal striae indicating subretinal fibrosis. In Coats's disease haemorrhages have been noted within the subretinal tissue as well as continuity of retinal vessels with those within the subretinal mass.⁵ In our study none of the eyes showed haemorrhage within the plaque, subretinal haemorrhage, retinal choroidal anasto-

mosis, pronounced serous retinal detachment, or macular drusen at any stage in a follow-up period of $2\frac{1}{2}$ to 9 years.

The hard exudate plaques, which measured 0.5 to 1.00 DD, showed complete resolution with organisation within 8 to 18 months, which occurred spontaneously in case 3 and as a response to photocoagulation in cases 1, 2, and 4. A pigment disturbance which may represent pigment epithelial proliferation was observed to develop beneath the resolving plaque in case 1, and was observed in case 3 at the first examination. In cases 3 and 4 (left eye) resolution and organisation of the foveal plaques preceded the complete absorption of hard exudates elsewhere in the macula. The fluorescein angiography appearance of the scar was consistent with the morphology previously described by us. The early phase of angiography showed a mottled hyperfluorescence from an intact choriocapillaris beneath a normal Bruch's membrane and pigment epithelium showing proliferation and degeneration with loss of pigment content. Discrete residual hyperfluorescence in the late angiograms resembled leakage from the choriocapillaris beneath the pigment epithelium, which was elevated by a serous detachment. Transmitted fluorescence due to depigmentation of pigment epithelium and leakage from diabetic retinal capillary disease within the scar contributed to the late appearance. We could observe no evidence of ingrowing choroidal neovascularisation or serous retinal detachment.³

In Dobree's study of the natural history of diabetic maculopathy² there were 14 eyes with plaques 0.5 DD or greater within the macula that were observed over an average interval of 4.1 years. Complete resolution occurred in 7 eyes, leaving a residue of marked pigmentation in 6 eyes and a central fibrous scar in 1 eye. There was significant visual improvement in 3 eyes, one of which recovered to 6/9 vision, no change in 3 eyes, and a deterioration from 6/25 to 6/60 in the eye showing scar tissue. The natural duration of the plaques was not specifically stated. In 3 of our 5 cases vision remained unchanged (6/60 to counting fingers at 1 metre) when scar tissue developed. Visual prognosis was good when the foveola was unaffected (case 1), and vision recovered from 6/120 to 6/15 in case 2 when the foveola was partly involved.

An understanding of the variable deposition and reabsorption of hard exudate has been derived from observations of circinate deposits which were observed to surround clusters of microaneurysms frequently.⁷ Fluorescein angiography studies⁸ and histochemical studies of hard exudate^{9,10} have provided evidence that most of the deposition results from focal plasma capillary leakage and that

the absorption takes place at the periphery where capillaries are less deranged, and by slow removal of the lipid component by phagocytosis. Morphologically in diabetic retinopathy large deposits of hard exudate collect mainly in the outer plexiform layer, surrounded by degenerative neuronal elements, with lipid-laden macrophages within and surrounding the exudate.⁹⁻¹² Degeneration of photoreceptors¹³ and continuity through the external limiting membrane with material beneath the retina have sometimes been observed.¹⁴ The deep accumulation of hard exudate in juxtaposition to the pigment epithelium may be a circumstance which causes focal alteration, perhaps metaplasia, in the pigment epithelium, which leads to organisation with scar formation. When severe retinal oedema is present, direct apposition of the plaque and the pigment epithelium may be prevented by an extension of the extracellular fluid into the subretinal space, which is difficult to detect biomicroscopically or by fluorescein angiography because of overlying cystoid changes. A reduction in leakage, either spontaneous after progressive capillary obliteration or after photocoagulation, accompanied by absorption of the thin layer of subretinal fluid, would lead to apposition and perhaps initiate the organisation of a deeply situated plaque by the pigment epithelium.

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Diabetic retinopathy in pregnancy: a 12-year prospective survey

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SUMMARY A prospective study extending over 12 years has surveyed 107 latent diabetics and 172 clinical diabetics during pregnancy. Among the clinical diabetics background retinopathy was evident or developed during pregnancy in 40 cases. Eleven cases showed proliferative changes, only 1 such case appearing *de novo* during gestation. There was a higher incidence of fetal loss in the diabetic than the latent diabetic group, and this loss was highest in those with proliferative retinal disease. Pregnancy was not associated with any increased risk to the mother of progression of retinal changes and visual loss. The only known direct relationship, namely, that between duration of diabetes and ocular complications, is confirmed.

A major fear of both doctor and patient has been that pregnancy in the diabetic may precipitate or aggravate retinopathy and lead to blindness. Because retrospective reports¹⁻³ have been conflicting, a prospective survey was begun in 1967 and has involved 279 patients up to 1978. The course of diabetic eye disease has been studied in relation to pregnancy, and eye ground signs have been evaluated, to see if they might in themselves be sufficient reason for termination of pregnancy. Findings from this study have been analysed and are now presented.

Patients and methods

Patients attending the antenatal clinics at the Royal Women's Hospital, Melbourne, who had latent or clinical diabetes were seen on a regular basis throughout their pregnancies. They were grouped into latent and clinical diabetics according to the recommendations of the World Health Organisation.⁴ Latent diabetics had either abnormal glucose tolerance tests or frank hyperglycaemia during pregnancy, the latter returning to normal after delivery. The clinical diabetics showed an abnormal response to the glucose tolerance test and symptoms or complications of diabetes.

At each visit, both during pregnancy and after delivery, a full routine ocular examination was made with special note of any retinopathy. Those

with overt retinopathy at their first visit were re-examined at intervals of 2 to 4 weeks, those with normal ocular fundi 4 to 8 weekly. Mothers were reviewed again in the puerperium and, where possible, 6 monthly thereafter. 107 latent diabetics were followed up through 119 pregnancies and 172 clinical diabetics through 227 pregnancies.

Over the last 3 years of the study all new patients were submitted to routine stereo fluorescein angiography some 6 months after delivery. Earlier patients who were still attending, and as many of the others who could be traced, were similarly examined—in all, a total of 93 patients. When the ophthalmoscopic and angiographic signs differed, angiographic pictures were taken as the basis for classification. It was made a general policy that this investigation was not performed during pregnancy.

The retinal appearances in the clinical diabetics were classified at the patient's first presentation as: normal, background, or proliferative. Included in background retinopathy were microaneurysms, varicose small vessels, retinal haemorrhages, retinal oedema and 'hard' and 'soft' exudates. Stereo angiographic signs included one or more of the following features: capillary bed obliteration, capillary aneurysms, vessel wall varicosities, and staining. When new vessels were seen on the retina, on the disc, or in the vitreous, the retinopathy was labelled proliferative.

The course of the retinopathy was classified under 3 headings: (1) *No overall change*. There was no observable change in clinical appearances or a

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Table 1 *Review attendance pattern—time related*

Follow-up	Latent diabetics	Clinical diabetics		
		No retinopathy	Background	Proliferative
Not after delivery	52	44	8	1
0-4 years after delivery	55	43	20	3
5-9 years after delivery	0	27	9	3
10+ years after delivery	0	11	3	0
Total	107	125	40	7
Mean follow-up period	2 years	5 years	6 years	4.5 years

Table 2 *Review attendance pattern—pregnancy-related*

	Latent diabetics	Clinical diabetics
During 1 pregnancy but not after delivery	42	39
During 1 pregnancy and after delivery	54	80
Through 2 pregnancies and after delivery	10	42
Through 3 or more pregnancies and after delivery	1	11
Total patients	107	172

The clinical diabetics have not been subdivided because of the variations in retinal appearances in different pregnancies.

waxing and waning of signs which negated change, as, for example, the appearance and subsequent disappearance of microaneurysms, exudates, or haemorrhages. (2) *Progression*. The criterion for progression was the appearance of new retinal lesions which persisted. The detection of a single capillary aneurysm in a previously normal fundus merited grading under this heading. (3) *Regression*. This term was applied where reduction or disappearance of pathological signs were recorded clinically or angiographically.

Results

The 279 patients comprised 172 clinical diabetics and 107 latent diabetics. The clinical diabetics were subdivided into 47 with retinopathy and 125 without. Sixty-four patients were seen in more than one pregnancy. Analysis of the review pattern is given in Tables 1 and 2. Of the 93 patients submitted to fluorescein angiography 12, whose retinæ were considered normal by ophthalmoscopic examination, were reclassified, on the photographic findings, as having background retinopathy.

Latent Diabetic Group

No patient showed retinopathy at the initial exami-

nation and none developed during pregnancy. Visual acuity at initial examination was 6/6 or better in both eyes of all 107 patients, apart from 4 who had minor refraction anomalies affecting one eye.

After delivery 5 patients became diabetic. Three of these showed no retinopathy after 3 years. The fourth developed background retinopathy within 4 years.

Clinical Diabetic Group

In this group 215 pregnancies were followed up, all but 3 patients being seen also in the puerperium. A further 12 patients were seen once only and failed to return for any ophthalmic examination after their initial visit.

NORMAL FUNDI

One hundred and twenty-five patients were found to have normal fundi (Table 3). Seven were seen only once by the ophthalmologist; the other 118 patients were followed up through at least one pregnancy. 123 patients had corrected acuities of 6/6 or better in both eyes at the time of initial examination. The other 2 each had an amblyopic eye. In 1 patient the vision dropped in one eye by 2 lines owing to the development of lens opacities. From among these 125 patients only 1 was observed to develop proliferative retinopathy and then not until some 10 years after the pregnancy. This retinopathy

Table 3 *Normal fundi at first examination*

Course during pregnancy	Course after delivery			
	Progress	No change	Regress	Lost to follow-up
Progression	13	2	3	5
No change	105	24	45	0
No record	7	—	—	—
Total	125			

regressed after photocoagulation and the patient has retained 6/6 vision in each eye.

BACKGROUND RETINOPATHY

Forty mothers were found to have background retinopathy at initial presentation (Table 4). They were followed up through 56 pregnancies. Five

failed to return after the first visit and a further seven were not seen after delivery. All but 2 of the cases had corrected vision of 6/6 or better in both eyes. Of these 2, 1 had 6/18 as a result of anisometropic amblyopia, the other 6/12 due to lens opacity. The fellow eyes each had acuities of 6/5. Vision remained stable in all patients who did not develop proliferative changes. There were 4 cases with background retinopathy which converted to proliferative. One patient developed new vessels in one eye during her pregnancy. In the other 3 proliferative changes were only noted after their pregnancies. The clinical details are set out in Table 5.

PROLIFERATIVE RETINOPATHY

Seven patients had proliferative retinopathy at their initial visit and were known to have had it before becoming pregnant for the first time. The features of these cases are summarised in Table 5.

Table 4 *Diabetics with background retinopathy*

Course during pregnancy	Course after delivery			
	Progress	No change	Regress	Lost to follow-up
Progression	11	4	1	2
No change	19	3	11	2
Regressed	5	1	2	0
No record	5	0	0	0
Total	40	8	17	3

Table 5 *Clinical details*

Age	Parity	Initial presentation		Change in pregnancy		Special therapy	Final result		Duration of diabetes	Outcome of pregnancy
		Fundi	VA	Fundi	VA		Fundi	VA		
27	1	R proliferans	6/12, 6/6	No change	6/12, 6/6	Nil	R vitreous haemorrhage 4 months after pregnancy	6/12, 6/6pt	24 years	Infant death pneumonia
18	1	R proliferans	6/5, 6/5	No change	6/5, 6/5	Nil	No follow-up	6/5, 6/5	10 years	Normal
27	1	R proliferans	6/6, 6/6	Bilateral vitreous haemorrhages	6/6, 6/6	Hypophysectomy after pregnancy	Haemorrhagic glaucoma	PL, HM	27 years	Stillbirth
30	1	Bilateral vitreous haemorrhages	6/18, 6/36	No change	3/60, 6/60	Hypophysectomy after pregnancy	Bilateral dense vitreous haemorrhages	PL, blind	17 years	Termination for hypertension
33	1	R proliferans	6/18, 6/5	No change	6/9, 6/6	Lost to follow-up			26 years	Neonatal death (premature)
28	2	R vitreous haemorrhages L proliferans	PL, 6/6	No change	PL, 6/6	Hypophysectomy during pregnancy	Initial regression but further new vessels developed 9 years after delivery	Blind 6/24 from cataract 6/9 pinhole	22 years	Normal
24	1	L proliferans	6/9, 6/12	No change	6/9, 6/12	Nil	Regression of new vessels but macular changes	6/6, 6/36	22 years	Normal
31	4	Background	6/5, 6/5	Progression	6/5, 6/5	Nil	Proliferans 2 years post partum	6/6, 6/60	26 years	Neonatal death
32	1	Background	6/6, 6/5	Proliferans L 3rd trimester	6/6, 6/5	Nil	Progression despite photocoagulation	6/6, 6/9	23 years	Normal
28	1	Background	6/6pt, 6/12pt	No change	6/6pt, 6/12pt	Nil	Proliferans 2 month post partum. Progression despite photocoagulation	6/6pt, No PL	24 years	Neonatal death
24	1	Background	6/9, 6/12pt	Macular oedema	6/9, 6/9	Photocoagulation during pregnancy	Proliferans 1 month post partum	6/6, 6/36	22 years	Normal

R = right, L = left, VA = visual acuity, PL = perception of light, HM = hand movements.

Table 6 Retinopathy related to age, duration of diabetes, parity, and fetal loss

Original description	Patients	Average age (years)	Average parity	Overall fetal loss per number of pregnancies	Average duration of diabetes (years)	% Fetal loss
Latent	107	33.6	3.6	8/119		6.7
Normal	118	28	2.8	34/164	8½	20.7
Background	40	28.2	2.7	9/56	13½	16.07
Proliferative	7	27.6	1.3	4/7	21	57.1

Table 7 Fetal and perinatal losses in clinical diabetics related to eye findings at initial visit and subsequent pregnancy

Pregnancy course	Original description								
	Normal			Background			Proliferative		
	Progression	No change	Not followed up	Progression	No change	Regression	Progression	No change	Regression
Pregnancies	15	144	5	11	40	5	1	5	1
Loss	7	23	4	2	6	1	1	3	0

MISCELLANEOUS CORRELATIONS

The proportion of patients with known renal disease or hypertension was the same in those who had retinopathy and in those with no retinopathy. Parity at the first visit was highest in the latent diabetics, who were also an older age group, and lowest in the proliferative retinopathy group. A significant correlation was noted between duration of diabetes and stage of retinopathy. The eye signs worsened with increasing duration of diabetes. Further analysis of this correlation in respect of age of onset of diabetes was not significant. The average ages of the patients in the different groups at the time when they were first seen or first developed retinopathy were not significantly different. These facts are tabulated in Table 6.

OUTCOME OF PREGNANCY

Latent diabetics

The fetal and perinatal death rate was lowest in this group, with 8 deaths out of 119 pregnancies.

Clinical diabetics

The clinical details of 47 fetal and perinatal deaths in the 227 pregnancies are shown in Table 7. There were significantly more problems in the clinical diabetics than among latent diabetics ($P < 0.002$), but the differences between the 3 groups of clinical diabetics were not statistically significant because of the small numbers in the proliferative group.

The reasons for termination of pregnancy were recorded as hypertension (2), nephritis (3), and toxæmia (1). In no patient was proliferative change considered the sole indication for terminating the

pregnancy. Hypertension was cited as the reason for termination of the pregnancy in 1 patient with proliferative retinopathy. One patient underwent pituitary ablation during pregnancy, yet gave birth to a normal child.⁵ The mortality figures include elective terminations, abortions, stillbirths, and deaths before 1 month of age.

The incidence of retinopathy in our study was 27% (47 of the 172 clinical diabetics who were examined). Beetham¹ reported a figure of 41%, Janert *et al.*² found 34%, and Cassar *et al.*⁶ recorded an incidence of 18%. The relationship between fetal and perinatal loss is correlated with eye findings in Table 7. Again the unfavourable prognosis associated with proliferative retinopathy is evident.

Discussion

A simple classification of retinopathy was deliberately adopted for this survey. An attempt to subdivide the retinopathy groups as was done in the Airlie House classification⁷ gave no further useful information because too few patients occupied each category. In the report on their survey of juvenile onset diabetes, Safir and Rogers⁸ made the same point. The 3 principal patterns of change in retinopathy observed in the present series, namely, progression, regression, and waxing and waning with no overall change, coincided with the findings from earlier studies of pregnant diabetics.^{1,3,9}

The 27% incidence of retinopathy in this prospective study, when compared with the figures of 41% reported by Beetham,¹ of 34% by Janert *et al.*,² and of 18% by Cassar *et al.*,⁶ probably reflects

improved diabetic management over the past 3 decades.

Ocular fundal photography and fluorescein angiography proved valuable in objective assessment of any changes, but the investigation was limited by poor co-operation, particularly from the latent diabetic group. This lack of co-operation may have been due to the fact that many of the patients were recent immigrants to Australia who changed address frequently and who could not be traced subsequently. The policy of not performing angiography during pregnancy provides an additional explanation for this low procedure rate.

At the macula angiography added to clinical observation in 2 ways: by delineating areas of capillary closure adjoining the normal avascular macular-foveal zone, and by demonstrating macular-foveal capillaries to a degree not found previously.¹⁰ It is important to record that no proliferative retinopathy was seen in the 4 eyes with macular-foveal capillaries, confirming that they are not a variety of intraretinal vascular proliferation.

In 3 of the 10 patients who were followed up through 3 pregnancies, disappearance of retinal microaneurysms was recorded and confirmed angiographically after the first pregnancy. Retinal signs remained stable throughout a subsequent pregnancy, but pathological changes reappeared before or during a still later pregnancy.

In the 1 patient followed up through 4 pregnancies retinopathy was seen during the first and third, but the signs had disappeared within the second and fourth pregnancies. Therefore such events cannot be related to the state of being pregnant but are most probably a reflection of the vicissitudes of diabetic microangiopathy. The lesions of diabetic retinopathy do fluctuate, and not infrequently changes occur in both directions at once, one part of the eye getting better, another part worse.¹¹

Progression or development of retinopathy during pregnancy occurred in 1 patient with proliferative retinopathy and in 11 patients with background retinopathy in our series. White^{3,9} found that in her series 11 developed proliferative retinopathy and 63 background retinopathy in 2147 pregnancies. Cassar *et al.*⁶ reported 1 patient who developed background retinopathy and 1 proliferative retinopathy during 92 pregnancies.

Our patients were graded on the retinal appearances at their initial visit, so that the data in our Table 7 suggests an unduly high rate of progression of retinopathy when compared with these other series.

Because the risk of progression of retinopathy during pregnancy was previously stated to be high, it had been suggested that diabetic women with any

retinopathy should be advised against pregnancy and that proliferative retinopathy was a specific indication for termination.^{1,12-14} However, the findings from our study confirm the view that the average course of proliferative retinopathy^{4,11,15-18} is not affected by pregnancy. One of our cases of proliferative retinopathy worsened in pregnancy. Five showed no change. Four background retinopathies converted to proliferative, only 1 during pregnancy. The proliferative retinopathies which progressed did so following pregnancy, 1 as late as 10 years after the delivery.

The use of photocoagulation in patients with proliferative retinopathy advancing during pregnancy has improved their prognosis.^{6,9} The 6 patients treated during the present study likewise benefited.

The present study found that proliferative retinopathy is associated with more than twice the fetal loss suffered by diabetic mothers with no retinopathy or with background changes. The link between proliferative retinopathy and increased fetal loss is well established.^{1,2,19,20} Severity of the retinopathy can be correlated with the presence of angiopathy elsewhere, especially in the kidneys.^{2,18,20} While the high incidence of fetal morbidity in mothers with proliferative retinopathy may provide supportive advice to terminate a particular pregnancy, the wide ranging suggestion by Okun *et al.*¹⁴ that proliferative retinopathy is a specific indication for termination of pregnancy requires modification. The results of the present study and the work of Cassar *et al.*⁶ establish that pregnancy per se does not lead to inevitable blindness even in the presence of proliferative retinopathy.

Close control of diabetes, especially during pregnancy, appropriate ocular therapy to prevent visual loss, and early admission to hospital for elective induction of labor or planned caesarean section^{2,6,9,15,19,20} now result in a reassuringly high percentage of healthy babies being born to seeing diabetic mothers. These facts, coupled with the general advances in neonatal intensive care, should allow informed, conservative optimism to dominate the 1980s in place of the gloomy prognostications given to earlier generations of diabetic women.

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Behaviour of untreated proliferative sickle retinopathy

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SUMMARY The development of ocular lesions in 313 patients with sickle cell disease followed up for periods of 1-8 years is described. Proliferative sickle retinopathy (PSR) was present on initial examination in 68 (12%) of 567 eyes and developed in a further 46 (8%) eyes during the study period. Spontaneous regression (autoinfarction) was present on initial examination in 33 (49%) eyes with PSR initially and developed in a further 45 (39%) eyes during the study. Development of PSR was more common in sickle cell-haemoglobin C (SC) disease, and autoinfarction appeared to occur more commonly in homozygous sickle cell (SS) disease. The two processes were delicately balanced, and some PSR lesions lasted less than a year before undergoing autoinfarction. Although the high prevalence of autoinfarction diminishes the clinical sequelae of PSR, blindness related to PSR occurred in 14/119 (12%) eyes. Autoinfarction closes the feeding vessels of PSR lesions more elegantly than, and without the complications associated with, photocoagulation. A greater understanding of factors involved in the progression and regression of PSR is relevant to defining the role of photocoagulation in this condition.

Vascular occlusion in the peripheral retina in sickle cell disease results in peripheral arteriolar obstruction with the development of arterio-venous fistulae and proliferative retinopathy.^{1,2} This sequence has been confirmed by angiography in longitudinal studies³ and occurs most frequently in sickle cell-haemoglobin C (SC) disease.⁴

Although proliferative sickle retinopathy (PSR) is common and may progress rapidly in some patients with SC disease, severe visual dysfunction is relatively uncommon.⁵ This anomaly may be reconciled, in part, by the tendency of PSR lesions to undergo autoinfarction,⁴⁻⁶ thus effectively curing the pathological circulation. Although representing progression in pathological terms, since further vaso-occlusion has occurred, autoinfarction reflects clinical improvement, as haemorrhage and possibly retinal detachment are rendered less likely. Autoinfarction occludes the lesions of PSR more elegantly than photocoagulation, and knowledge of this complication is relevant both to defining the role of photocoagulation and to understanding the natural history of sickle cell retinopathy. The

balance between progression and regression (autoinfarction) also determines the clinical outcome of sickle cell eye disease. We present here, longitudinal observations on groups of patients with sickle cell syndromes followed up for periods up to 8 years.

Material and methods

Many patients from the Sickle Cell Clinic at the University Hospital of the West Indies have had ophthalmological examinations during the period 1970-78. Longitudinal observations, implying a minimum of 2 examinations at yearly intervals, were available in 313 patients (Table 1). A trial of light coagulation in PSR was conducted between 1973 and 1978 by treating the worst affected eye in 54 of these patients. Five blind eyes prohibiting retinal examination were also excluded from the description of retinal findings. This report describes the behaviour of retinal vessel disease in control eyes of the treatment series and in both eyes of patients not admitted to the treatment series excluding the 5 blind eyes detailed above (567 eyes in 313 patients).

The diagnosis of homozygous sickle cell (SS) disease, sickle cell-haemoglobin C (SC) disease, sickle cell- β^+ thalassaemia ($S\beta^+$ thal), and sickle cell- β^0 thalassaemia ($S\beta^0$ thal), were based on criteria

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Table 1 Summary of repeated ophthalmological examinations performed at approximately yearly intervals at sickle cell clinic

Genotype	Total patients	Number of ophthalmological examinations								Patient/years of observation
		2	3	4	5	6	7	8	Total	
SS	115	76	21	13	2	2	1	—	296	460
SC	157	58	32	22	20	16	6	3	562	669
S β^+ thal	25	19	2	—	—	2	2	—	70	82
S β^0 thal	14	8	4	—	1	1	—	—	39	58
SO Arab	1	—	1	—	—	—	—	—	3	5
SD Punjab	1	1	—	—	—	—	—	—	2	3
Total	313	324	180	140	115	126	63	24	972	1277

described elsewhere.⁷ Patients with sickle cell-haemoglobin O Arab (SO Arab) disease and sickle cell-haemoglobin D Punjab (SD Punjab) disease were identified by haemoglobin structural studies.

Ophthalmological examination included visual acuity, direct and indirect ophthalmoscopy through dilated pupils, retinal drawings in all patients, and retinal photography and fluorescein angiography where indicated. The extent of proliferative sickle retinopathy was recorded as the number of lesions and also the degree of circumferential and meridional involvement.

Results

Proliferative sickle retinopathy, defined either by leakage of intravenously administered fluorescein or by occluded fibrotic lesions, was present on initial examination in 68 eyes of 56 patients (14 SS; 37 SC; 4 S β^+ thal; 1 SO Arab disease) and developed

de novo during the period of observation in a further 46 eyes of 41 patients (10 SS; 28 SC; 1 S β^+ thal; 2 S β^0 thal). The prevalence of PSR at initial examination and arising de novo during the study is expressed as a proportion of the total number of patients in the longitudinal study in Table 2.

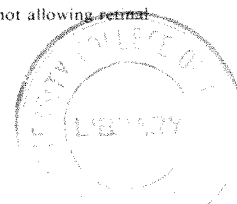
Progression, denoted by an increase in the number or size of existing PSR lesions (20 eyes) or development of PSR lesions de novo (46 eyes) occurred in 66 eyes of 59 patients (12 SS; 43 SC; 2 S β^+ thal; 2 S β^0 thal) during the observation period. The mean age of patients showing progression in the 4 genotypes was 32.4, 27.7, 29.0, and 29.0 years respectively, with a median age in SC disease of 24 years. Rate of progression varied markedly, one patient developing 11 new PSR lesions in 18 months whereas another had gradual development or enlargement of a single lesion over 6–8 years.

There was a tendency for the most rapid progres-

Table 2 Prevalence of proliferative sickle retinopathy on admission to, and occurring de novo during, the longitudinal study

Genotype	Total examined		Proliferative sickle retinopathy					
			On initial examination		Arising de novo during study		At end of study	
	Patients	Eyes*	Patients	Eyes	Patients	Eyes	Patients	Eyes
SS	115	221	14 (12%)	16 (7%)	10 (9%)	13 (6%)	23 (20%)	29 (13%)
SC	157	270	37 (24%)	45 (17%)	28 (18%)	30 (11%)	63 (40%)	75 (28%)
S β^+ thal	25	46	4 (16%)	5 (11%)	1	1	5 (20%)	6 (13%)
S β^0 thal	14	26	0	0	2	2	2	2
SO Arab	1	2	1	2	0	0	1	2
SD Punjab	1	2	0	0	0	0	0	0
Total	313	567	56 (18%)	68 (12%)	41 (13%)	46 (8%)	94 (30%)	114 (20%)

*Excluding 54 eyes included in trial of light coagulation (8 SS; 40 SC; 4 S β^+ thal; 2 S β^0 thal) and 5 blind eyes (1 SS; 4 SC) not allowing retinal examination.



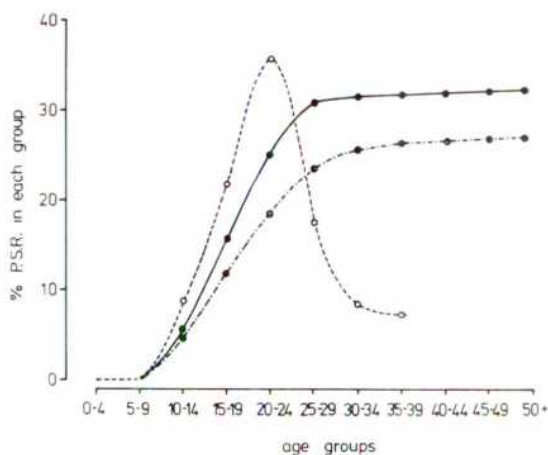


Fig. 1 Prevalence of PSR according to age in different groups of patients with SC disease.
 ○ — — — ○ PSR developing de novo.
 ⊙ — — — ⊙ Cumulative prevalence of PSR in longitudinal study.
 ● — — — ● Cumulative prevalence of PSR in cases showing progression.

sion to be apparent in young patients. In the 12 patients with SS disease showing progression 19 new lesions occurred in 4 patients under the age of 25 years (mean 4.8 lesions/patient) compared to 15 new lesions in 8 patients over this age (mean 1.9 lesions/patient). Similarly, in 43 patients with SC disease, 58 new lesions developed in 18 patients

under the age of 25 years (mean 3.2 lesions/patient) compared to 53 in 25 patients over this age (mean 2.1 lesions/patient). Analysis of the age distribution of patients with SC disease developing PSR for the first time indicated that the highest risk period, accounting for 36% of cases, was 20–24 years (Fig. 1). Two-thirds of patients developing PSR de novo were in the 15–29 age group, which included only 46% of the total patient group. Young patients also showed the most florid progression of PSR lesions, as illustrated in Fig. 2.

Regression, denoted by avascular PSR lesions, was apparent on initial examination in 33 eyes of 26 patients (10 SS; 13 SC; 2 $S\beta^+$ thal; 1 SO Arab disease) and cessation of perfusion of individual PSR lesions was observed during the study period in 45 eyes of 39 patients (11 SS; 24 SC; 2 $S\beta^+$ thal; 2 $S\beta^+$ thal), 9 eyes of which also had avascular lesions on initial examination. Of the 114 eyes with PSR 31 (27%) showed complete autoinfarction and 38 (33%) partial autoinfarction by the end of the study period. Complete autoinfarction was commoner in eyes showing no increase in PSR during the study period (19 eyes), but also occurred in eyes showing an increase in PSR (2 eyes) and in those developing PSR de novo (10 eyes). Partial autoinfarction occurred in 16, 12, and 10 eyes of the 3 groups respectively. The prevalence of autoinfarction of PSR lesions in eyes of the different genotypes is summarised in Table 3. The average age of patients observed to be undergoing auto-

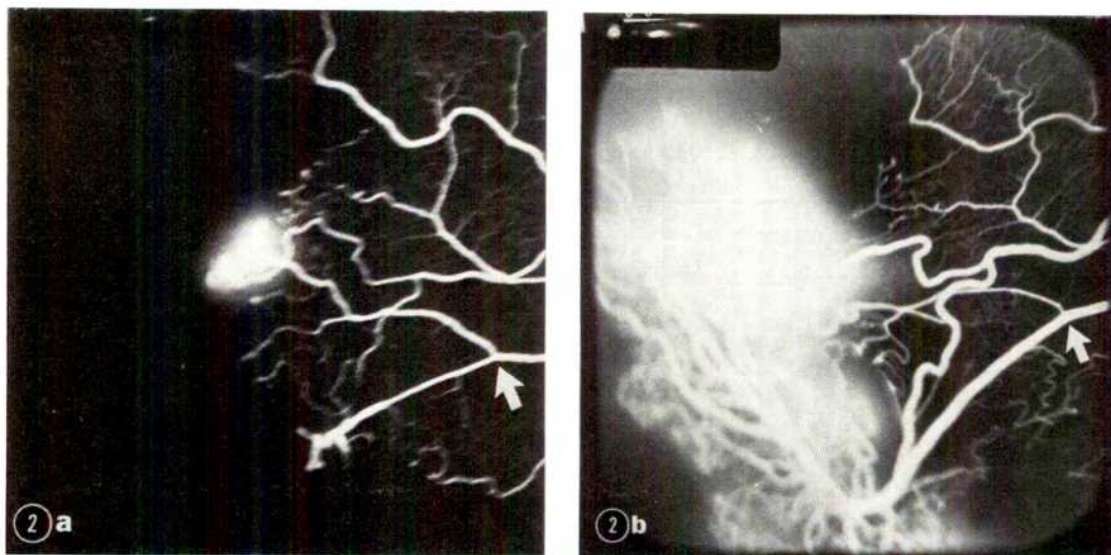


Fig. 2 17-year-old female with SC disease demonstrating rapid progression from (a) to (b) 16 months later. Dynamic developments have changed the relative calibres of vessels. Arrows indicate the same vessel bifurcation.

Table 3 Prevalence of autoinfarction of proliferative sickle retinopathy on admission to, and occurring during, the longitudinal study

Genotype	Totals affected by PSR		Autoinfarction					
			On initial* examination		Arising during study		At end of study†	
	Patients	Eyes	Patients	Eyes	Patients	Eyes	Patients	Eyes
SS	23	29	10 (71%)	10 (63%)	11 (48%)	13 (45%)	17 (74%)	19 (66%)
SC	63	75	13 (35%)	18 (40%)	24 (38%)	28 (37%)	32 (51%)	41 (55%)
Sβ ⁺ thal	5	6	2	3	2	2	4	5
Sβ ⁻ thal	2	2	0	0	2	2	2	2
SO Arab	1	2	1	2	0	0	1	2
Total	94	114	26 (46%)	33 (49%)	39 (41%)	45 (39%)	56 (60%)	69 (61%)

*Percentages expressed as proportion of those with PSR on initial examination. †Totals may not add up because some patients fall in both categories.

infarction was 32.2 years (SS), 29.6 years (SC), 29.0 years (Sβ⁺thal), and 33.0 years (Sβ⁻thal). The average age of patients attaining complete autoinfarction was 39.2 years (SS) and 35.2 years (SC).

A variety of mechanisms contributed to autoinfarction, of which the commonest was occlusion of the arteriolar feeding vessels as part of a centripetal arteriolar retraction (Fig. 3). This process might occur even in extensive circumferential involvement by PSR (Fig. 4) and was occasionally associated with simultaneous progression in the

same eye. Avulsion of an optic disc PSR occurred in 1 patient with SC disease (Fig. 5), resulting in a massive vitreous haemorrhage which subsequently cleared to 6/12 visual acuity. In 2 patients haemorrhage into the PSR lesion appeared to precipitate regression of the lesion, and in 2 other patients vitreous traction of PSR lesions probably compromised flow in the feeding arterioles.

The balance of the processes of progression and regression in the current study are summarised in Fig. 6. Examples of the pattern of progression and

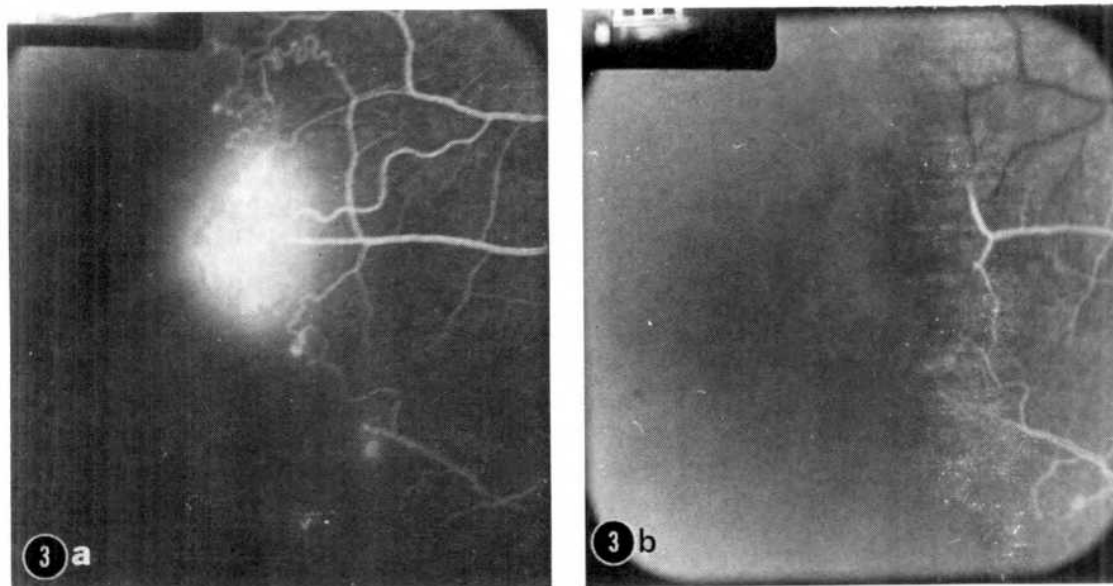


Fig. 3 21-year-old male patient with SS disease. Fluorescein angiogram of right temporal periphery indicates leaking lesion (a) with subsequent disappearance 2 years later (b).

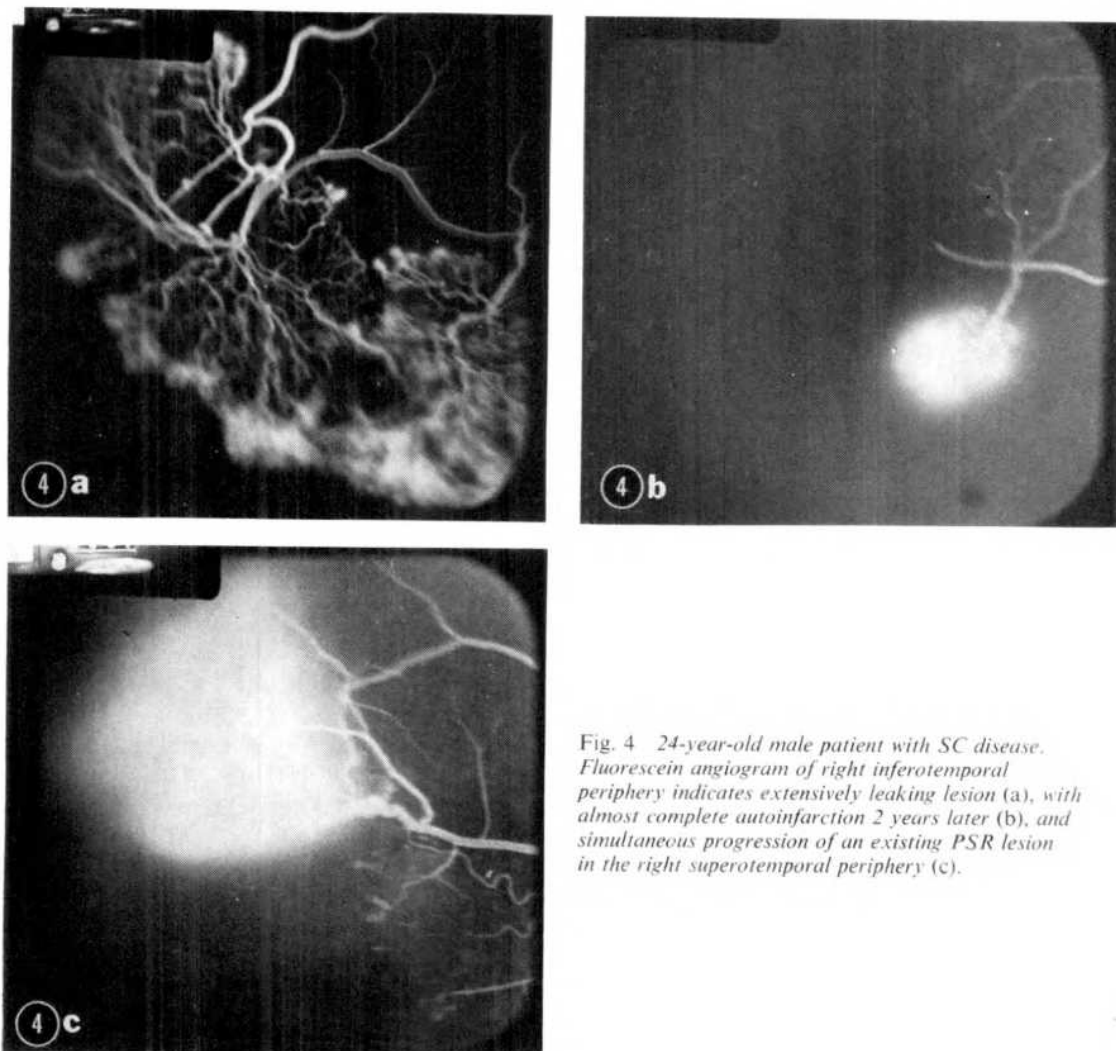


Fig. 4 24-year-old male patient with SC disease. Fluorescein angiogram of right inferotemporal periphery indicates extensively leaking lesion (a), with almost complete autoinfarction 2 years later (b), and simultaneous progression of an existing PSR lesion in the right superotemporal periphery (c).

regression in individual patients are illustrated in Fig. 7. Individual PSR lesions were observed to develop and undergo autoinfarction during the study period in 19 eyes, lesions lasting less than 2 years in 10 eyes and less than 7 months in 3 eyes.

Proliferative sickle retinopathy showed no change in 10/29 (34%) eyes in SS disease, 19/75 (25%) in SC, 4/6 (67%) $S\beta^+$ thal, and 2/2 (SO Arab disease) over periods of 71, 40, 17, and 10 eye/years of observation respectively. Stability tended to be a feature of older patients, mean ages being 47, 44, 53, and 46 years in the 4 genotypes respectively.

A history of, or signs compatible with, vitreous haemorrhage was present in 20 eyes of 17 patients (5 SS; 11 SC; 1 $S\beta^+$ thal), and occurred during the study period in 9 eyes. Retinal haemorrhage without

vitreous involvement occurred in 5 eyes affected by PSR and in an additional 3 eyes without PSR but in which PSR subsequently developed. Vitreous haemorrhage was followed by autoinfarction of PSR lesions in 15/20 eyes affected, all lesions in the affected eye being occluded in 6 of these.

A visual acuity of $<6/60$ on admission to the study was probably attributable to PSR in 12 eyes of 11 patients (3 SS; 7 SC; 1 SO Arab). In 5 of these eyes retinal examination was impossible, but a history of traction retinal detachment and previous surgery suggested a diagnosis of proliferative retinopathy. In 2 eyes acuity improved with the resolution of a vitreous haemorrhage, and acuity deteriorated to $<6/60$ during the study in a further 4 eyes of 4 patients. Acuity of $<6/60$ at the end of

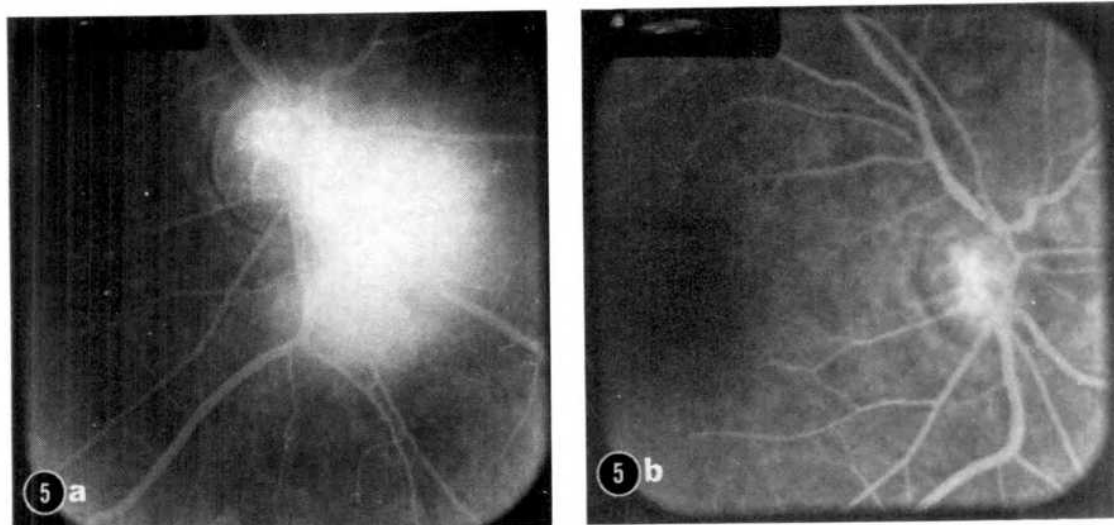


Fig. 5 33-year-old male patient with SC disease. Fluorescein angiogram of right optic disc indicates leaking PSR lesion (a) which subsequently avulsed 18 months later (b).

the study was attributed to PSR in 14 eyes, giving an overall prevalence of PSR related blindness in 14/119 or 12%. The age at blindness from presumed PSR related disease varied from 22 to 58 years, with half occurring between 22 and 28 years.

Discussion

Ocular examinations were initially performed on random patients unselected on the basis of ocular pathology, but repeated examination and hence

inclusion in the longitudinal study was more likely in patients showing proliferative retinopathy. This ocular selection and the exclusion of 54 eyes with PSR entered in a separate photocoagulation study implies that the figures for prevalence of PSR on admission must be treated with caution. However, the progression of PSR, its development de novo, and its autoinfarction may be validly observed in this patient group.

The recording of serial changes provides problems, and no system is entirely satisfactory. Clinical parameters such as changes in visual acuity are too gross and insensitive as an index of progression. Retinal disease may be defined in terms of circumferential as well as meridional involvement from the ora serrata backwards, but this is also gross and difficult to document. Counting the number of PSR lesions may ignore the size of the lesion, a minute leaking lesion subtending 1–2° of the retinal circumference or continuous PSR occupying 360° of the circumference both being regarded as 1 lesion. This anomaly may be reduced in continuous circumferential involvement by referring to each 30° segment of PSR as a single 'lesion', and so 360° involvement would constitute 12 'lesions'. Coalescence of multiple lesions may reduce the total number yet represent progression, whereas autoinfarction of a single lesion may leave 2 perfused areas, thereby increasing the number of 'lesions' yet representing regression. Despite these shortcomings the ability to record PSR in a numerical and analysable form does have advantages.

Factors contributing to the development of PSR

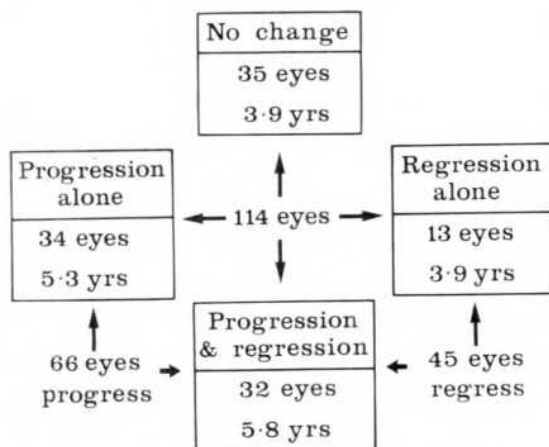


Fig. 6 Summary of the change observed during the study period in the 114 eyes affected by PSR. Mean duration of follow-up in each group indicated by lower figure in each box.

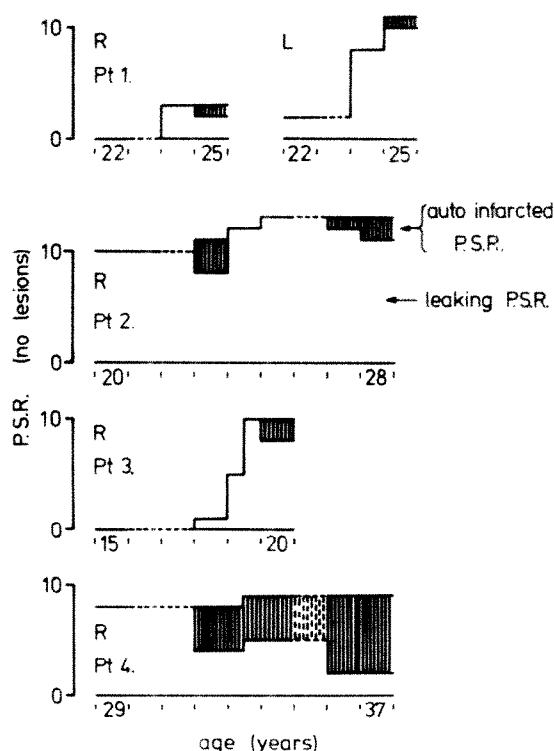


Fig. 7 Occurrence of leaking and auto-infarcted P.S.R. lesions in 5 eyes of 4 patient with SC disease. Dotted line represents the period before an episode for which ocular examinations were not available and during which the subsequent episode may have occurred.

are beginning to be understood.⁸ The high prevalence in the SC and S β ⁺thal genotypes suggests the role of a high haematocrit, and there is a highly significant relationship with total haemoglobin, the prevalence of PSR rising steeply with haemoglobin levels above 12 g/dl. Whole blood viscosity rises in proportion to the square of the haematocrit, and the effect of high haemoglobin levels is probably explained by the increased viscosity and impairment of blood flow in small vessels. There is also a positive relationship between PSR and mean cell volume, suggesting that the MCV or a related haematological index may also influence peripheral blood flow. PSR also increases with age, which might be expected, since age reflects the duration of the vaso-occlusive process, and the effects of vaso-occlusion are cumulative. However, the present study has identified an additional effect of age in the particularly rapid progression of PSR in the 15–29 year age group. Further analysis of haematological data is required to determine whether this

effect is mediated through haematological changes at this age or is independent of them.

It was the apparent conflict between the rapidly progressive vascular disease observed in some young adults and the relative infrequency of severe visual dysfunction in older patients that suggested that spontaneous regression of lesions may be common.² This has been amply confirmed by the present report, which indicates evidence of autoinfarction in 69/114 (61%) of eyes with PSR by the end of the study period. The peak incidence of observed autoinfarction followed approximately 2 years behind the peak incidence of PSR lesions *de novo*, and average ages of patients demonstrating progression and regression were 32.4 and 32.2 years in SS and 27.7 and 29.6 years in SC disease respectively. The close temporal relationship observed between the development of PSR and its autoinfarction in many patients explains to some extent the relative infrequency of severe visual dysfunction. Autoinfarction renders PSR lesions less likely to haemorrhage and hence less likely to cause visual impairment.

The commonest cause of autoinfarction is probably progressive centripetal retraction of retinal vascular arcades,⁶ but a close relationship of autoinfarction and vitreous haemorrhages was noted in 15 eyes in the present study. Three-quarters of patients developing vitreous haemorrhages were subsequently found to have autoinfarcted PSR lesions. Whether spontaneous occlusion of feeder vessels precipitated haemorrhage from necrotic PSR lesions or whether primary haemorrhage resulted in vaso-occlusion is at present unclear.

Autoinfarction reduces the likelihood of complications from proliferative retinopathy, but severe visual impairment may still occur. Central visual loss related to PSR occurred during the study period in 4/114 eyes with PSR and was present in 14/119 (12%) eyes at the end of the study. Although self-limiting to some extent, therefore, PSR still represents a highly significant cause of visual loss in sickle cell disease.

The ability of PSR lesions to undergo autoinfarction raises questions on the role of photocoagulation in this condition. This procedure is usually capable of closing feeder vessels and rendering lesions avascular but is not without risk, and may cause serious complications such as chorioretinal neovascularisation. Spontaneous autoinfarction achieves the same results more elegantly and without risk of many of the complications. However, cases prone to autoinfarction may still develop clinical visual impairment before this occurs. Before the role of photocoagulation in this condition can be defined, a greater understanding of the natural history of sickle cell eye disease, especially the

mechanisms and factors contributing to auto-infarction, is necessary.

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Follow-up study of detachment of the retinal pigment epithelium*

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SUMMARY To determine the clinical course of untreated retinal pigment epithelial detachment we reviewed data from 50 eyes of 42 patients followed up for an average of 29 months without photocoagulation. In 14 eyes with avascular lesions, in patients under 50 years of age, all had a final vision of 20/30 or better. None developed neovascularisation or haemorrhage. In 17 eyes with avascular lesions in patients aged over 50, 8 (47%) flattened spontaneously. Five (24%) developed neovascularisation, 2 of which became haemorrhagic, with vision of less than 20/200. In 19 senile eyes with vascular lesions 14 (74%) had a final vision of 20/200 or less. The prognosis in eyes with pigment epithelial detachments is related to the age of the patient and the presence of choroidal neovascularisation. Photocoagulation is seldom needed for pigment epithelial detachments in young patients. Its value in senile eyes is unproved.

Detachment of the pigment epithelium results from the accumulation of fluid derived from the choriocapillaris, either directly or from new vessels extending into the subpigment epithelial space.¹ While photocoagulation has been used to flatten these lesions,²⁻⁴ their course when left untreated has not been well documented. We reviewed data from untreated eyes with pigment epithelial detachments which were studied with fundus photography, fluorescein angiography, and frequent follow-up examinations.

Materials and methods

Fluorescein angiograms performed at the Wilmer Institute and the Boston University Medical Center during the years 1968 through 1974 were reviewed. All those with avascular serous detachments of the pigment epithelium in the macula, as described by Gass,¹ were selected. Also chosen were all eyes with pigment epithelial detachments accompanied by choroidal neovascularisation⁵ in

patients over 50 years of age. Information was then obtained from the patient's clinical records.

Fifty eyes of 42 patients met the following criteria and are the subject of this report: (1) clinical and fluorescein angiographic evidence of pigment epithelial detachment; (2) good quality fluorescein angiogram; (3) no photocoagulation treatment; and (4) minimum follow-up period of 6 months.

Eyes included in this study were not subjected to photocoagulation for one of the following reasons: (1) evaluation took place prior to 1970, which is when laser photocoagulation was first employed in the treatment of macular disorders at the Wilmer Institute; (2) evaluation was performed at the Wilmer Institute subsequent to 1973, when a strictly conservative treatment approach was adopted; (3) the patient was evaluated at the Boston University Medical Center as part of a study of the natural history of macular diseases; or (4) the patient was under the care of an ophthalmologist who did not feel photocoagulation was of any benefit in this disorder.

Details of the initial examination, along with clinical and angiographic features of the lesion, were recorded. This included visual acuity, size of pigment epithelial elevation (disc diameters), distance from the fovea (defined as the centre of the retinal

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avascular zone on fluorescein angiography), and the presence of sensory retinal detachment, haemorrhage, lipid, drusen, or choroidal neovascularisation.

Most patients had frequent follow-up examinations with repeat fundus photography and fluorescein angiography on at least 1 occasion. In a few instances follow-up information was provided by the patient's referring ophthalmologist.

For purposes of analysis eyes were separated into 3 groups based on the age of the patient and the presence of choroidal neovascularisation at the time of the initial examination. Group 1 (nonsenile) consisted of eyes from patients under 50 years of age. None had angiographic evidence of choroidal

neovascularisation. Group 2 (senile, avascular) was made up of eyes from patients 50 years of age and older, without choroidal neovascularisation. Group 3 (senile, vascular) comprised eyes from patients 50 years of age and older in which the presence of choroidal neovascularisation was demonstrated by fluorescein angiography.

Results

GROUP 1 (NONSENILE)

Fourteen eyes of 11 patients were followed up for 8 to 51 months (average, 23 months) (see Table 1). Nine patients were male and 2 female. The age range was 37 to 47 years (average, 43 years). Five were right eyes and 9 were left eyes. The size of the pigment epithelial detachment varied from one-third disc diameter to 1 disc diameter. One eye had 3 detachments, 1 eye had 2 detachments, and the remaining eyes had 1 detachment each. One lesion was directly beneath the fovea, and 9 were one-fourth disc diameter or more from the fovea. Three eyes had a readily apparent detachment of the overlying sensory retina. Minimal drusen were present in 1 eye, but haemorrhage and lipid were present in no eyes. Initial visual acuity was 20/20 or better in 8 eyes, 20/25–20/30 in 4 eyes, and 20/40 or worse in 2 eyes.

During the follow-up period pigment epithelial detachments flattened spontaneously in 7 eyes, leaving a mild degree of pigment disturbance at the site of the lesion. In the remainder of the eyes the detachments persisted and were accompanied by pigment derangement over the dome of the detachment. Haemorrhage did not occur in any eye, and none developed evidence of choroidal neovascularisation. Visual acuity remained the same or improved in all 14 eyes. Eight eyes had a final vision of 20/20 or better, 4 eyes were 20/25, and 2 eyes were 20/30.

GROUP 2 (SENILE, AVASCULAR)

Seventeen eyes of 13 patients were followed up for 14 to 86 months (average, 35 months). There were 6 males and 7 females. The age range was 53 to 76 years (average, 64 years). There were 6 right eyes and 11 left eyes. One eye had two detachments, and the remainder had 1 each. The size of the pigment epithelial detachment varied from one-half to 3 disc diameters. Nine were 1 to 1½ to 3 disc diameters. One was 3 disc diameters. The lesion extended beneath the fovea in 12 eyes and was less than one-fourth disc diameter from the fovea in 5 eyes. A sensory retinal detachment was present in 6 of the 17 eyes. In all patients drusen were present in the involved and/or fellow eye. The initial visual acuity

Table 1 Data from 50 eyes with pigment epithelial detachment

	Group 1	Group 2	Group 3
	Nonsenile	Senile, avascular	Senile, vascular
No. of eyes	14	17	19
Right:left	5:9	6:11	11:8
No. of pts.	11	13	18
Male:female	9:2	6:7	11:7
Avg. age and range	43 (37–47) yr	64 (53–76) yr	67 (55–82) yr
Avg. follow-up (mo)	23 (range 8–51)	35 (range 14–86)	29 (range 6–75)
Initial examination:			
Size of detachment (disc diameters)	1/3 to 1	1/2 to 3	1/2 to 3
Neovascularisation (eyes)	0	0	19
Drusen (eyes)	1	15	19
Haemorrhage (eyes)	0	0	4
Lipid (eyes)	0	0	9
Neuroepithelial detachment (eyes)	3	6	19
Visual acuity (eyes):			
20/20–20/40	13	14	9
20/50–20/100	1	3	5
20/200–or less	0	0	5
Course (eyes):			
Flattened	7 (50%)	8 (47%)	0
Unchanged	7 (50%)	7 (41%)	5
Haemorrhage/scar	0	2 (12%)	15
New vessels	0	5 (24%)	19
Final visual acuity:			
20/20–20/40	14 (100%)	9 (53%)	1 (5%)
20/50–20/100	9	6 (35%)	4 (21%)
20/200 or less	9	2 (12%)	14 (74%)
Same or better than initial vision	14 (100%)	10 (59%)	2 (11%)

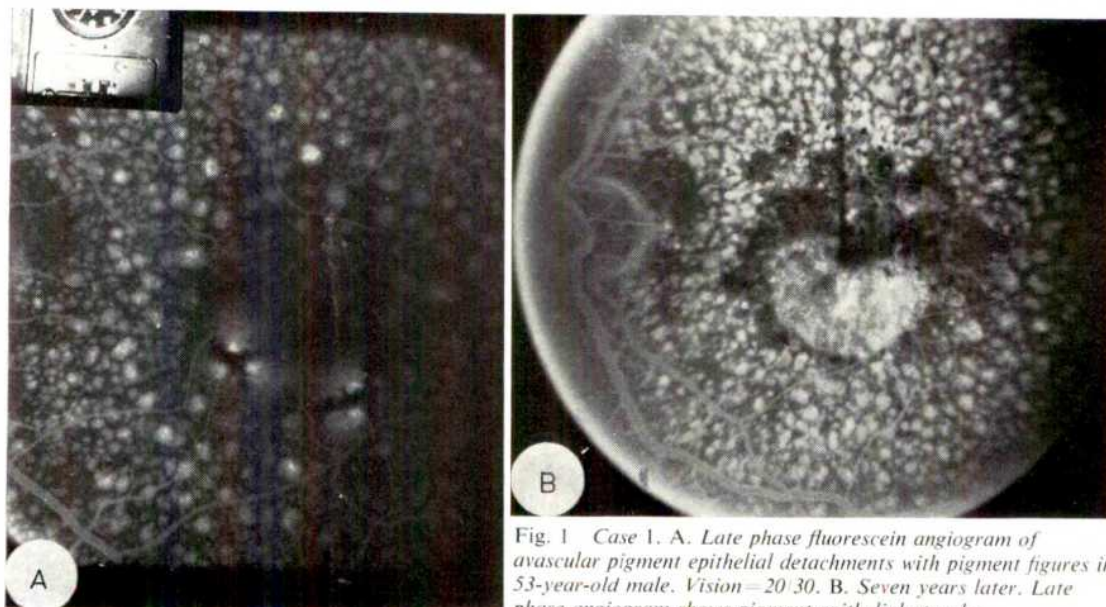


Fig. 1 Case 1. A. Late phase fluorescein angiogram of avascular pigment epithelial detachments with pigment figures in 53-year-old male. Vision = 20/30. B. Seven years later. Late phase angiogram shows pigment epithelial atrophy.

was 20/40 or better in 14 eyes and 20/50 to 20/100 in 3 eyes.

During the follow-up period the retinal pigment epithelium (RPE) detachment flattened completely in 8 of the 17 eyes, resulting in varying degrees of atrophy of the pigment epithelium (Fig. 1b). In 7 eyes the RPE detachment persisted and was accompanied by progressive pigment disturbance, including the formation of pigment figures over the dome of the detachment. In the remaining 2 eyes the lesion became haemorrhagic, resulting in severe visual loss. In these 2 eyes choroidal neovascularisation was presumed to have developed, but this was not documented with follow-up fluorescein angiography. In 3 other eyes neovascularisation was present on follow-up angiography. In 1 eye this occurred beneath a persistent pigment epithelial detachment, and in 2 eyes it developed temporal to the detachment, which had spontaneously flattened (Fig. 2).

Visual acuity deteriorated (2 lines or more on the Snellen chart) in 7 of the 17 eyes (41%) over the study period. Final vision was 20/40 or better in 9 eyes, 20/50 to 20/100 in 6 eyes, and 20/200 or worse in 2 eyes. Of 6 eyes with large detachments (2 disc diameters or more) 3 eyes had a final vision of 20/40 or better, 1 eye was 20/60, and 2 eyes were worse than 20/200.

GROUP 3 (SENILE, VASCULAR)

Nineteen eyes of 18 patients were followed up for 6 to 75 months (average 29 months). There were 11 males and 7 females. The age range was 55 to 82

years (average, 67 years). There were 11 right eyes and 8 left eyes. All eyes had subpigment epithelial neovascularisation demonstrated by fluorescein angiography, and were accompanied by a detachment of the sensory retina. Haemorrhage was present in 4 eyes. Neovascularisation was located beneath the fovea in 7 eyes. Drusen were present in the involved and/or fellow eye in all cases. Lipid was noted beneath the retina in 9 eyes. Initial visual acuity was 20/20 to 20/40 in 9 eyes, 20/50 to 20/100 in 5 eyes, and 20/200 or less in 5 eyes.

During the study period increasing haemorrhage and/or scar formation occurred in 15 of the 19 eyes. Final visual acuity was 20/40 or better in one eye, 20/40 to 20/100 in 4 eyes, and 20/200 or less in 14 eyes.

Discussion

There is only minimal information describing the clinical course of eyes with untreated pigment epithelial detachments. Lewis⁶ reported follow-up data from 32 eyes of 21 patients with untreated serous detachments of the pigment epithelium. All patients were under 55 years of age (average age, 45 years), and there was no accompanying evidence of senile macular degeneration or other ocular disease. 97% of the eyes had final visual acuity of 20/50 or better after an average follow-up period of 7 years. Similarities in the characteristics and the relatively benign clinical course of this condition to those of central serous choroidopathy were noted.

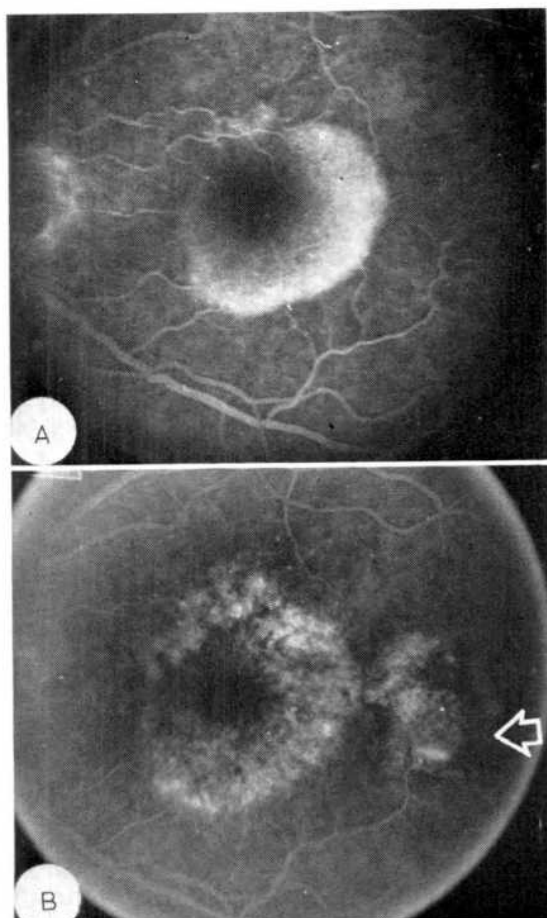


Fig. 2 Case 2. A. Late phase angiogram of avascular pigment epithelial detachment in 71-year-old male. Vision=20/20. B. Two years later. Late phase angiogram shows flat retinal pigment epithelium atrophy in area of previous detachment with haemorrhagic subretinal neovascular lesion temporally (arrow). Vision=20/25.

Gass² observed 7 older patients with serous pigment epithelial detachments of 1–2 disc diameters accompanied by drusen. He reported that without treatment these patients maintained visual acuity for periods of up to 2 years. Teeters and Bird,⁷ however, in their study of untreated senile eyes reported a poor visual prognosis. They found that 61% of eyes with avascular lesions had a final vision of 6/60 or less. In eyes with vascular lesions the visual outcome was worse.

We studied pigment epithelial detachments in eyes of young adults as well as those occurring in older individuals.

In Group 1 (nonsenile), all patients were under 50 years of age and displayed essentially no accom-

panying fundus pathology. The lesions were small (1 disc diameter or less) and initial visual impairment was minimal. During the course of the study period the detachments either flattened spontaneously (50%) or remained elevated. None developed choroidal neovascularisation or haemorrhage. The final vision was 20/30 or better in all eyes.

As noted by Lewis,⁶ this group may well be considered a form of central serous choroidopathy in which the pigment epithelial detachment, rather than an overlying sensory retinal detachment, is the predominant feature. Indeed, 3 eyes showed an accompanying sensory retinal detachment, each of which resolved during the course of the study period. The male to female ratio of 9:2, and the self-limited nature of the lesion, with minimal permanent visual loss, is similar to that found in patients with classical central serous choroidopathy.^{8–10}

In group 2 (senile, avascular) the natural course was variable, and significant visual impairment sometimes occurred. All patients were over 50 years of age, and all eyes displayed drusen, a recognised precursor of further senile macular degenerative changes.^{2,11}

Teeters and Bird⁷ reported 18 eyes with avascular disciform lesions studied with fluorescein angiography, and followed up for four to 19 months (average, 10 months). During this period 12 eyes (67%) developed angiographic evidence of neovascularisation. Complete resolution of the detachment occurred in only 3 eyes (16%). Eleven eyes (61%) had deteriorated to a final vision of 6/60 or worse.

Our findings, representing data from 17 eyes with avascular detachments, followed up for an average of 35 months, produced a better prognosis. Five eyes (29%) developed evidence of choroidal neovascularisation, while 2 eyes (12%) deteriorated to 20/200 or less during the study.

These conflicting results probably arise from differences in interpretation of choroidal neovascularisation of the fluorescein angiogram. In each of the 17 eyes studied by us the pigment epithelium detachment filled with dye in a nearly uniform and complete fashion. This was not true in some of the eye studies by Teeters and Bird.⁷ In their description of the avascular process lesions were included which, on fluorescein angiography, showed irregular filling and uneven late hyperfluorescence.^{7,12} We feel that these eyes already had new vessels, and thus the natural course and ultimate visual results were unfavourably influenced. We recognise, however, that new vessels might also be present in eyes which we have classified as avascular with fluorescein angiography. Sarks¹³ has demonstrated the rather common occurrence of choroidal new vessels in senile eyes examined histologically at necropsy,

even in those without antecedent clinical evidence of their presence.

Our study indicated that avascular pigment epithelial detachments in the senile population differ from those occurring in nonsenile eyes. They tend to be larger, are associated with diffuse degenerative changes in the posterior pole, and in some instances may progress to a neovascular process with possible haemorrhagic sequelae. Those that flattened spontaneously (47%) resulted in varying degrees of pigment epithelial disturbance. In some cases this became progressively more pronounced long after flattening of the lesion. Mild to moderate visual impairment generally occurred in these eyes.

In group 3 (senile, vascular) definite evidence of neovascularisation was demonstrated by fluorescein angiography in all eyes. This course was one of progressive deterioration, with 15 of the 19 eyes experiencing further haemorrhage and/or scar formation. The remaining 4 eyes showed no improvement during the study period. The visual outcome was poor, with 14 of the 19 eyes (74%) becoming legally blind. These poor results are similar to those reported by Teeters and Bird.⁷ They contrast markedly with the excellent visual prognosis found in avascular detachments in nonsenile eyes (group 1), and the variable outcome in avascular detachments in senile eyes (group 2).

It is of interest to consider the role of photocoagulation in the light of these findings.

With regard to the eyes in group 1 (nonsenile), it would seem that similar guidelines to those recommended for the treatment of central serous choroidopathy are indicated.¹⁰ Unless further benefits become established, photocoagulation should be considered only for those patients in whom visual impairment is disabling or annoying, assuming the lesion is located a safe distance from the fovea.

The value of photocoagulation for eyes in group 2 (senile, avascular) remains uncertain. Bird⁴ reported the flattening of 21 of 24 avascular detachments following photocoagulation. Visual results were relatively good, with 67% of these eyes achieving 6/12 vision, while none were 6/60 or worse after an average 10-month follow-up period. Gass,³ however, noting that most detachments could be flattened with photocoagulation, found visual results to be variable.

Considering the poor visual prognosis of eyes in group 3 (senile, vascular) one is tempted to consider such eyes for photocoagulation, with heavy focal treatment applied to extrafoveal neovascular membranes. Bird⁴ has reported encouraging results by employing heavy applications of argon laser energy to neovascular membranes as close as one-eighth

disc diameter from the fovea. However, because these eyes have diffuse involvement of the choroid, Bruch's membrane, and pigment epithelium, photocoagulation, even if successful, may be of only temporary benefit.

Conclusion

The clinical course of untreated retinal pigment epithelial detachment varies with the age of the patient and the presence of choroidal neovascularisation. In nonsenile eyes the visual prognosis is excellent. In senile eyes with avascular lesions the visual outcome is variable, with approximately half of all eyes experiencing moderate to severe visual impairment. In senile eyes with vascular lesions the visual prognosis is poor.

Photocoagulation is seldom indicated for lesions in nonsenile eyes. Its value in the treatment of senile eyes is unproved and could best be determined by a prospective, randomised clinical trial. Such a trial is now in progress in the United Kingdom.

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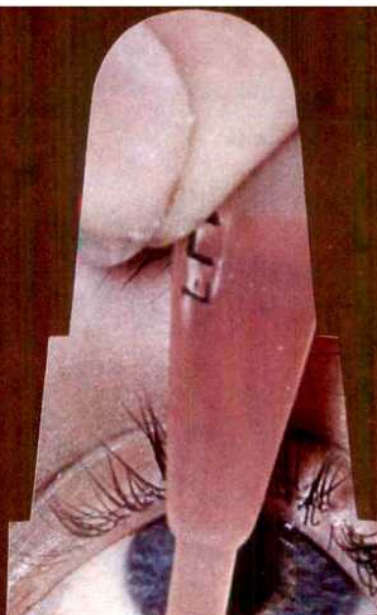
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Hyoscine (Scopolamine)
Hydrobromide Ph. Eur. | 0.2% |
Phenylephrine (Metaoxedrine)
Hydrochloride B.P. | 10% |
Tropicamide B.P. | 0.5% | 1% |

MIOTICS

- Pilocarpine
Nitrate Ph. Eur. | 1% | 2% | 3% | 4% |

LOCAL ANAESTHETICS

- Amethocaine (Tetracaine)
Hydrochloride Ph. Eur. | 0.5% | 1% |
Benoxinate (Oxybuprocaine)
Hydrochloride | 0.4% |

COMBINED LOCAL ANAESTHETIC AND STAIN

- Lignocaine (Lidocaine)
Hydrochloride Ph. Eur. | 4% |
& Fluorescein Sodium B.P. | 0.25% |

STAINS

- Fluorescein Sodium B.P. | 2% |
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Retinal detachment in congenital glaucoma

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SUMMARY This paper reports the occurrence of retinal detachment in 18 patients suffering from congenital glaucoma. Difficulty in establishing control of the glaucoma and the presence of high myopia were common findings. The poor results of detachment surgery were related to opacities in the media preventing evaluation of the retinal details and the development of massive preretinal retraction.

Detachment of the retina complicating congenital glaucoma was first described by Axenfeld,¹ who considered that the detachment was often the determining factor in the production of blindness in this condition. Knapp² also reported this development in an 11-year-old child with advanced anterior segment changes of congenital glaucoma; he considered that degenerative changes within the vitreous were implicit in the development of retinal detachment.

Cases of congenital glaucoma complicated by retinal detachment have also been mentioned within surveys of juvenile detachment.³⁻⁵ In these series a total of 11 cases of congenital glaucoma were encountered among 672 cases of retinal detachment within the first 2 decades of life.

This report concerns 18 patients with retinal detachment associated with congenital glaucoma. The clinical characteristics of these detachments and the salient features of the associated glaucoma are described together with the results of retinal detachment surgery. The incidence of retinal detachment in a closely studied series of patients with simple congenital glaucoma is also reported.

Patients and methods

We reviewed the clinical records of 189 patients with congenital glaucoma involving 290 eyes who were treated at Moorfields Eye Hospital between 1960 and 1979. Thirteen eyes of 11 patients suffered a retinal detachment. In addition 7 patients presented during this same period with retinal detachment in association with congenital glaucoma which had been managed elsewhere.

The glaucoma was classified as either simple or complicated. Simple congenital glaucoma refers to

cases which do not have any other developmental anomaly, either ocular or systemic, and show typical gonioscopic appearances.⁶ Complicated congenital glaucoma refers to cases in which glaucoma is related to other developmental defects of the eye with or without extraocular abnormalities.

A detailed profile of each patient was constructed from the clinical records, and particular attention was directed to the following factors: age of onset of glaucoma; family history of glaucoma or retinal detachment; glaucoma surgery undertaken and the control of intraocular pressure achieved; the maximum corneal diameter recorded and the refractive error; the age at which the patient developed retinal detachment, the type and extent of the detachment, and the nature of retinal breaks and other retinal abnormalities encountered; the retinal status of the fellow eye; retinal surgery undertaken and the results achieved.

Results

Retinal detachment occurred in 21 eyes of 18 patients with congenital glaucoma of varying aetiology. There were 13 males and 5 females. The details of the glaucoma and the principal features of the retinal detachments are presented in Table 1.

Congenital glaucoma was classified as simple in 16 and complicated in 2 of our patients. The age of onset of glaucoma ranged from 3 weeks to 12 months and was bilateral in 16 and unilateral in 2 cases. Glaucoma surgery was undertaken in 18 eyes of 16 patients, including filtering procedures in 10 eyes. Surgery was not performed on 1 eye with simple glaucoma which had undergone spontaneous arrest and both eyes of a patient with bilateral Sturge-Weber syndrome. Satisfactory control of the glaucoma was achieved in 10 eyes of 11 patients.

The interval between the onset of glaucoma and

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Table 1 Clinical details of congenital glaucoma and retinal detachment in 18 patients

Case	Onset of glaucoma and classification	Glaucoma surgery	IOP control	Diameter cornea (mm)	Refractive error Dph eq	V/A	Age at detachment	Presentation	Features of detachment	Surgery	Results	Associated findings
1, M L	R 5 Months simple L	G×3 TR×1 G×3	Poor Fair	15 15	-12.50 -11.00	HMs 6/36	6 Yr —	Hypotension —	Total/no breaks —	Inoperable —	— —	Cataract —
2, F L	R 4 Months simple L	G×3 G×3	Good Good	14 14	-16.00 -19.00	6/60 6/36	— 7 Yr	— Visual loss	Temporal half round holes and multiple dissections 80° —	— 1. Local explant 2. Encirclement 3. Para plana vitrectomy	— Failed MPR	Amblyopia —
3, M L	R 6 Months simple L	G×1 G×1	Poor Good	14.5 13	-7.00 -9.50	6/60 6/9	8 Yr —	Vitreous haemorrhage —	Total/no breaks —	Enucleation —	— —	Rubeosis Iridis bullous keratopathy
4, M L	R 2 Months simple L	G×4 T×1 C×1 G×2 C×1	Poor Poor	13.5 13.5	-2.50 -3.50	6/60 CFs	6 Yr 9 Yr	Hypotension Hypotension	Total/no breaks Total/no breaks	Inoperable Inoperable	— —	Cataract/luxation Cataract/luxation
5, M L	R 4 Months simple L	G×3 G×4	Fair Fair	14 13	-15.00 -20.00	3/60 6/60	2 Yr 5 Yr	Hypotension Hypotension	Total/no breaks Total/360° giant tear	Encirclement Inoperable	Failed MPR —	Cataract —
6, M L	R 6 Months simple L	G×3 G×1	Fair Good	16 14	-11.00 -9.00	6/60 6/12	8 Yr —	Hypotension —	Total/no breaks —	Inoperable —	— —	Cataract —
7, M L	R 1 Month simple L	G×3 G×2 S×1 CA×1	Poor Poor	14.5 14.5	-4.00 Not known	— PL	8 Mth —	Hypotension —	Total/no breaks —	Inoperable —	— —	Corneal scarring cataract Bullous keratopathy
8, F L	R 10 Months simple L	G×3 S×1 G×2 S×1 T×1	Poor Poor	13 13	-8.00 -4.50	6/60 CFs	— 14 Yr	— Postop finding	Total/no breaks choroidal detachment	Inoperable —	— —	— —
9, F L	R 2 Months simple L Normal	G×3 T×1 —	Fair —	13.5 11.5	-9.00 -0.50	6/60 6/6	14 Yr —	Visual loss —	Total/upper temporal U tear —	Encirclement and local explant —	Failed MPR —	Amblyopia —

G=Goniotomy, TR=Trabeculectomy, C=Cyclocryotherapy, CA=Cyclocauterisation, S=Scheie's thermocauterisation, I=Iridencleisis.

Table 1 Continued

Case	Onset of glaucoma and classification	Glaucoma surgery	IOP control	Diameter cornea (mm)	Refractive error Dsph eq	VA	Age at detachment	Presentation	Features of detachment	Surgery	Results	Associated findings
10, M	R 1 Month simple	G x 3	Fair	14.5	Not known	—	—	—	—	360° prophylactic cryotherapy	—	Corneal scarring Cystoid degeneration of ora serrata
L		G x 2	Fair	13.5	-8.00	—	4 Yr	Visual loss	Total/270° giant dialysis	Encirclement, pars plana vitrectomy, silicone oil	Upper half reattachment	Lens subluxation
11, M	R 3 Weeks simple	T x 1	Fair	13	Not known	—	3 Yr	Hypotension	Total/no breaks	1. Encirclement 2. Silicone oil	Success	Corneal scarring
L		T x 1	Poor	13.5	Not known	—	—	—	—	—	—	Bullous keratopathy
12, M	R 3 Months Axenfeld's syndrome	G x 4 S x 3 C x 1	Poor	14	-10.00	HMs	10 Yr	Hypotension	Inferior half single U tear	Local explant	Failed MPR	—
L		G x 2 T x 1	Poor	15	-2.50	6/60	—	—	—	—	—	—
13, F	R 2 Months bilateral Sturge-Weber syndrome	Nil	Good	13.5	+1.50	6/60	6 Yr	Vitreous haemorrhage	Total serous	Silicone oil	Failed I/O haem. Success	Choroidal haemangioma
L		Nil	Good	13.5	+1.50	6/60	6 Yr	Vitreous haemorrhage	Total serous	Silicone oil	—	Choroidal haemangioma
14, F	R Not known simple Normal	Nil spont. arrest	Good	14	+11.50	CFs	24 Yr	Visual loss	Temporal half single U tear	Encirclement	Failed	Aphakia
L		—	—	11.5	+0.50	6/12	—	—	—	—	—	—
15, M	R 12 Months simple	I x 1	Good	13.5	-10.00	6/60	14 Yr	Visual loss	Temporal half 90° giant tear	1. Local explant 2. Silicone oil	Failed MPR	—
L		I x 1	Good	14	-8.00	6/60	—	—	—	—	—	Amblyopia
16, M	R 2 Months simple	I x 1 CD x 1 I x 1	Fair	14	-8.00	6/60	32 Yr	Visual loss	Total 180° giant dialysis	Scleral resection	Failed MPR	—
L			Good	13.5	-8.00	6/24	—	—	—	—	—	—
17, M	R 8 Months simple	G x 2	Good	13	-2.50	6/12	—	—	Flat U tear	Prophylactic cryotherapy Encirclement	—	—
L		G x 1 S x 1	Fair	13.5	-10.00	CFs	8 Yr	Visual loss	Total/no breaks	—	Failed	Amblyopia
18, M	R 4 Months simple	I x 1	Good	13.5	+11.00	CFs	—	—	—	—	—	Aphakia
L		I x 1	Good	13	+5.00	6/36	33 Yr	Visual loss	Total, round hole UNQ	Encirclement	Success	—

G = Goniotomy. TR = Trephine. T = Trabeculectomy. C = Cyclocryotherapy. CA = Cycloaenisation. S = Scheie's thermocauterotomy. I = Iridencleisis. UNQ = Upper nasal quadrant.

the development of retinal detachment ranged from 7 months to 33 years. The presenting features of retinal detachment included ocular hypotension with or without lens subluxation in 9 eyes, subjective visual loss in 8 eyes, vitreous haemorrhage in 3 eyes, and the observation of retinal detachment shortly after filtering surgery in 1 eye. A wide range of refractive errors was encountered. Of a total of 18 eyes in which the error could be measured 15 eyes were found to have myopia in excess of 2.50 dioptres and in 8 eyes to be 10 or more dioptres as expressed in spherical equivalents.

Retinal detachment was unilateral in 15 and bilateral in 3 cases. With the exception of serous detachments in both eyes of the patient with bilateral Sturge-Weber syndrome the detachment was considered to be rhegmatogenous in all cases. However, retinal breaks were identified in only 9 eyes and included u-tears in 4 eyes, round holes in the temporal periphery with multiple incomplete dialyses in 1 eye, giant pre-equatorial tears in 2 eyes, and giant dialyses in 2 eyes.

Retinal detachment surgery was undertaken in a total of 13 eyes of 12 patients. The limited potential for useful visual recovery together with the presence of significant corneal and lens opacities were the major factors precluding any attempt at surgical management in the remaining 8 eyes. Encirclement with or without additional silicone sponge explants was performed in 8 eyes and local procedures alone in 3 eyes. Silicone oil injection was used in 3 eyes with massive preretinal retraction. Pars plana vitrectomy for massive preretinal retraction was performed on 2 eyes.

In 3 eyes detachment surgery was successful as defined by retinal reattachment for 6 months or longer following surgery. In 2 of the 5 eyes in which silicone oil injection was used anatomical reattachment with visual improvement was achieved. The causes of failure of detachment surgery included severe intraocular haemorrhage in one eye and massive preretinal retraction in 8 eyes.

Cases classified as complicated congenital glaucoma included a patient with Axenfeld's syndrome which proved extremely resistant to all forms of attempted glaucoma control and the case of bilateral Sturge-Weber syndrome. The latter patient developed bilateral serous retinal detachments in association with diffuse choroidal angiomas (Fig. 1). The only treatment considered likely to achieve retinal reattachment was the use of silicone oil injection. In the left eye a successful result was achieved whilst surgery of the right eye was complicated by the development of severe intraocular haemorrhage.

The retinal status of the fellow eye was assessed



Fig. 1 Central horizontal B-scan section of right eye showing retinal detachment and choroidal haemangioma (arrow).

wherever possible. In one eye a flat u-tear in temporal retina was identified for which prophylactic cryotherapy was undertaken. In a further case the fellow eye of a patient with a giant retinal dialysis showed marked cystoid degeneration of the ora serrata in all quadrants, which was treated by 360° cryotherapy.

Twelve eyes of 10 patients in this study belonged to a closely studied series of 158 cases of simple congenital glaucoma involving 246 eyes followed by the late A. Lister and one of the authors (N.S.C.R.). The results of surgery and the overall complications within this series have been the subject of a previous report.⁷ Over a follow-up period ranging from 2 to 19 years this represents an incidence of retinal detachment of 6.3%.

Discussion

Early reports of retinal detachment in congenital glaucoma concerned eyes severely compromised by the effects of uncontrolled glaucoma.^{1,2} An increased risk of retinal detachment was thought to accompany surgical intervention in cases of uncontrolled glaucoma.² However, there have been few reports of this complication in patients observed over a prolonged period following the introduction of more effective methods of glaucoma control.

Myopia is the most common refractive error in congenital glaucoma and is usually between 1 and 7 dioptres.⁸ The axial length and the degree of myopia are not constantly related, since the anticipated myopia is mitigated by changes in corneal curvature and posterior displacement of the lens. Myopic fundus changes in hydrophthalmia were described by Parsons⁹ and included retinal pigment atrophy and disc crescents. Myopia was an almost constant finding in our patients, exceeding 10 dioptres in 8 of the eyes. This excess of highly myopic eyes

implies significant accelerated axial growth, though we did not determine the axial length of the eyes.

With a single exception all patients received miotic therapy at some stage in their clinical course. No significant association between the use of miotics and the development of retinal detachment was recognised. None of the patients were known to have received irreversible cholinesterase inhibitors, which might be considered inappropriate in cases of advanced uncontrolled glaucoma with the attendant risk of retinal detachment.

The features of congenital glaucoma commonly encountered in our patients included bilateral involvement and the necessity for repeated surgical intervention. These patients are commonly found within the estimated 15% of all patients with simple congenital glaucoma who are not effectively controlled by goniotomy alone.⁷ Serious impairment of vision was often present before the onset of retinal detachment as a result of anterior segment changes and glaucomatous optic nerve damage. However, in several cases the fellow eye also had poor visual function attributed to severe corneal scarring, dense amblyopia, or glaucomatous optic atrophy.

In 19 of 21 eyes the retinal detachment was considered to be of rhegmatogenous origin, though retinal breaks were only identified in 9 eyes. The presence of corneal scarring or cataract precluded visualisation of retinal details in many cases. Of the retinal breaks that were identified, vitreoretinal traction played a predominant role in their origin. Giant retinal breaks were located at varying distances from the ora serrata but in all instances appeared to be pre-equatorial. Giant retinal breaks have been described in association with various developmental anomalies.^{5, 9, 10}

The results of detachment surgery in cases of congenital glaucoma are frequently disappointing in our experience. Of a total of 13 eyes considered likely to benefit from detachment surgery a successful outcome was achieved in only 3 eyes of 3 patients. The major factors contributing to these poor results were the difficulty in the evaluation of peripheral retinal details owing to opacities in the ocular media and the tendency to develop massive preretinal retraction. Evidence of the latter was often detected at the time of presentation, and postoperatively several eyes proceeded rapidly to an inoperable state. In 5 eyes the only surgical technique con-

sidered likely to achieve retinal reattachment was silicone oil injection, and a successful result, that is, more than half of the retina reattached accompanied by visual improvement, was achieved by this method in only 2 eyes.

Prolonged follow-up of patients suffering from congenital glaucoma has identified a variety of factors which may limit the visual outcome or prejudice continued visual function. These include amblyopia,¹¹ delayed recurrence of glaucoma, and late endothelial decompensation necessitating keratoplasty.¹² Retinal detachment is a further complication which may develop in buphthalmic eyes at varying intervals after the onset of glaucoma and would appear to carry an extremely poor prognosis.

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Effect of hypercapnea and hyperventilation on human intraocular pressure during general anaesthesia following acetazolamide administration

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SUMMARY The changes in intraocular pressure due to blood pH, PCO_2 , and PO_2 alterations induced by hyperventilation and hypercapnea in man undergoing routine general anaesthesia were studied. It was shown that hypercapnea produces elevation of intraocular pressure, while hyperventilation lowers it. Acetazolamide pretreatment did not alter these IOP responses to PCO_2 , PO_2 , and blood pH changes.

Several factors, especially drugs, influence the intraocular pressure during general anaesthesia. All these are evaluated during intraocular surgery or in the determination of intraocular pressure in children. Among them the effect of hypercapnea and hyperventilation has not been sufficiently elucidated yet. Changes in intraocular pressure due to blood pH alterations are well known, and the IOP-decreasing effect of diabetic acidosis and coma has been reported since the beginning of the century. Recently interest in the correlation between the blood pH and intraocular pressure has increased. Duncalf and Weitzner,¹ Beaugié and Samuel,² and Kieler *et al.*³ have shown either in dogs or in man the IOP-increasing effect of hypercapnea as well as the decreasing effect of hyperventilation. On the other hand Krupin *et al.*⁴ have proved that acidosis, induced by intravenous administration of HCL, lowers the intraocular pressure in rabbits, while alkalosis, due to intravenous administration of Na bicarbonate, increases it. These 'contradictory' observations support a hypothesis that probably different mechanisms are involved in the IOP responses to blood pH changes, depending on the causes of these pH changes.

In the present paper we study the effect of different blood pH, PCO_2 and PO_2 on human intraocular pressure induced by primary respiratory mechanisms (hyperventilation, hypercapnea) during general anaesthesia. And the effect of oral acetazolamide

pretreatment on these IOP responses is also investigated.

Patients and methods

Twenty-four patients, of both sexes, aged 28 to 54 years, scheduled for various routine operations (in the supine position) under general anaesthesia were used in this study. They were selected from others after a complete examination (either systemic or ophthalmological) in order to exclude any possibility that the achieved pH 'borderline' values could have any side effects on them. All patients were premedicated with atropine (0.6 mg) and meperidine (75 mg). Anaesthesia was induced with thiopentone sodium. An endotracheal tube was inserted after pancuronium (4 mg) given intravenously. As is well known, these drugs only slightly affect the intraocular pressure. Anaesthesia was maintained with $\text{N}_2\text{O} + \text{O}_2$ in 5:2 mixture under control of ventilation. Respiratory alkalosis was achieved by hyperventilation manually and respiratory acidosis by insufficient administration of oxygen and isolation of the soda-lime circuit. During the operation the pulse rate and blood pressure were continuously determined, and ECG was recorded as well. Arterial blood samples were collected from the radial artery and analysed for PCO_2 , PO_2 , and pH values by an automatic analyser (Radiometer, Copenhagen). The intraocular pressure was measured by means of the Perkins handheld tonometer, using fluorescein strips. Benoxinate ophthalmic solution 0.4% was used for corneal anaesthesia before induction of general anaesthesia.

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The patients were divided in 2 groups. 14 (group I) underwent our standard experimental protocol: IOP determination before induction to anaesthesia, immediately after that, half an hour later, when the patients were in 'maximal' alkalosis, and finally

half to 1 hour later, when the 'maximal' acidosis was achieved. Also, immediately after induction of anaesthesia as well as during alkalosis and acidosis the blood pH, P_{CO_2} , and P_{O_2} were determined. In 10 more patients (group II), we repeated the same procedures 1 hour after a single dose of acetazolamide (500 mg) given orally. Intraocular pressure was also determined just before acetazolamide administration.

All results are expressed as the arithmetic mean $\pm$ the SD of the mean. Student's *t* test (paired) was used for the statistical evaluation of the results.

Results

As Fig. 1 shows there was a slight decrease of intraocular pressure after induction of anaesthesia compared to the premedication values, due to administration of barbiturates and pancuronium. Under general anaesthesia half an hour after induction the achievement of respiratory alkalosis (pH: 7.46, P_{CO_2} 30 mmHg and P_{O_2} 112 mmHg) produced a marked fall in the intraocular pressure (average of both eyes 4.5 mmHg), which is highly significant ($P < 0.01$). Finally, when respiratory acidosis was achieved (pH 7.27, P_{CO_2} 49 mmHg and P_{O_2} 95 mmHg), the intraocular pressure was elevated (average of both eyes 7 mmHg) significantly ($P < 0.001$).

In the second set of experiments the same procedures were repeated 1 hour after acetazolamide administration. The mean IOP value of 10 patients, in whom the intraocular pressure was measured before premedication and acetazolamide administration, was decreased significantly (average of both eyes 4.6 mmHg ($P < 0.001$) after induction to anaesthesia. This was mainly due to acetazolamide pretreatment as well as to barbiturates and pancuronium administration (Fig. 2). Respiratory alkalosis (pH 7.47, P_{CO_2} 28.5 mmHg and P_{O_2} 122 mmHg) achieved half an hour after induction of anaesthesia further decreased the intraocular pressure (average of both eyes 2.5 mmHg). After that, half an hour to 1 hour later, an increase of intraocular pressure occurred (average of both eyes 6.25 mmHg) when respiratory acidosis was attained (pH 7.26, P_{CO_2} 53.5 and P_{O_2} 96 mmHg). This elevation of intraocular pressure is statistically highly significant ($P < 0.001$). Thus the preadministration of acetazolamide did not alter the IOP responses to blood pH, P_{CO_2} , and P_{O_2} changes. The changes in intraocular pressure during either alkalosis or acidosis in both phases of experiments were observed in every case, and so every patient acted as his own control.

The effects of either alkalosis or acidosis on

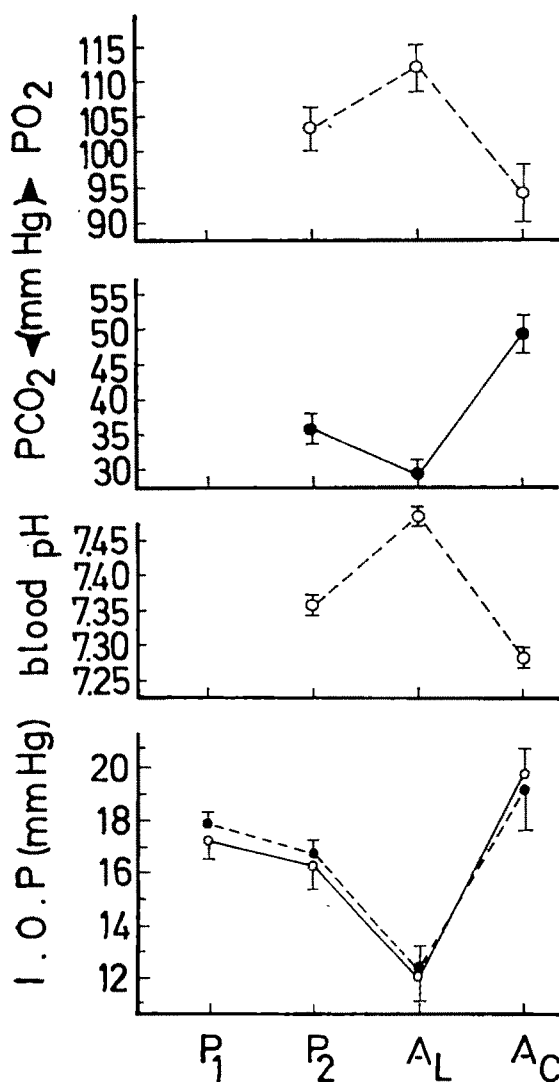


Fig. 1 Intraocular pressure changes due to blood pH, P_{CO_2} , and P_{O_2} alterations induced by primary respiratory mechanisms during general anaesthesia (number of observations=14; vertical bars=SD of the mean). P_1 =before induction of anaesthesia and P_2 =immediately after that (baseline measurements). A_L =alkalosis, hyperventilation (roughly 1/2 hour after induction). A_C =acidosis, hypercapnea (approximately 1 hour after induction of anaesthesia and usually near recovery time).

intraocular pressure were not associated with changes in blood pressure and heart rate, which did not vary significantly to affect the intraocular pressure throughout the operation time.

Discussion

From these data we can conclude that P_{CO_2} alterations result in changes of intraocular pressure, which are not preventable by acetazolamide administration. Respiratory alkalosis decreases the intraocular pressure, while respiratory acidosis increases it. Our results are consistent with those of prior studies of intraocular pressure changes due to P_{CO_2} alterations in man and dogs.^{1,5} Partial disagreement with the results of Wistrand and Maren⁶ in rabbits is probably due to different experimental procedures. We also confirmed the opinion of Beaugié and Samuel² and Kielar *et al.*³ that the blood pH is neither a sensitive nor a determining factor in regard to IOP changes. So blood pH can fall with either rise or fall of intraocular pressure and vice versa (see baseline pH values on Fig. 1 and 2 and compare with IOP values on the same figures). Metabolic acidosis due to diabetic ketosis, severe muscular exercise, and acid or acetazolamide administration lowers intraocular pressure and also blood pH.^{4,7-10}

On the other hand respiratory acidosis, due to an increase of end-tidal CO_2 in a closed-circuit rebreathing system^{3,5} or to hypoventilation and isolation when using soda-lime circuit (as we did) lowers blood pH but increases the intraocular pressure. All these, as well as the fact that metabolic acid/base equilibrium disturbances are partially compensated by respiratory mechanisms and vice versa, could explain the apparent controversies about the results of the effects of these disturbances on intraocular pressure due to respiratory or metabolic causes.

The mechanism(s) of IOP elevation associated with P_{CO_2} increase is not clear yet. Increased venous pressure^{1,5} and/or increased uveal blood

flow¹¹ are the most likely explanations. Trying to prevent this IOP rise induced by increased P_{CO_2} , and in order to investigate whether or not an active secretion mechanism is also involved, we tested the effect of acetazolamide on IOP rise due

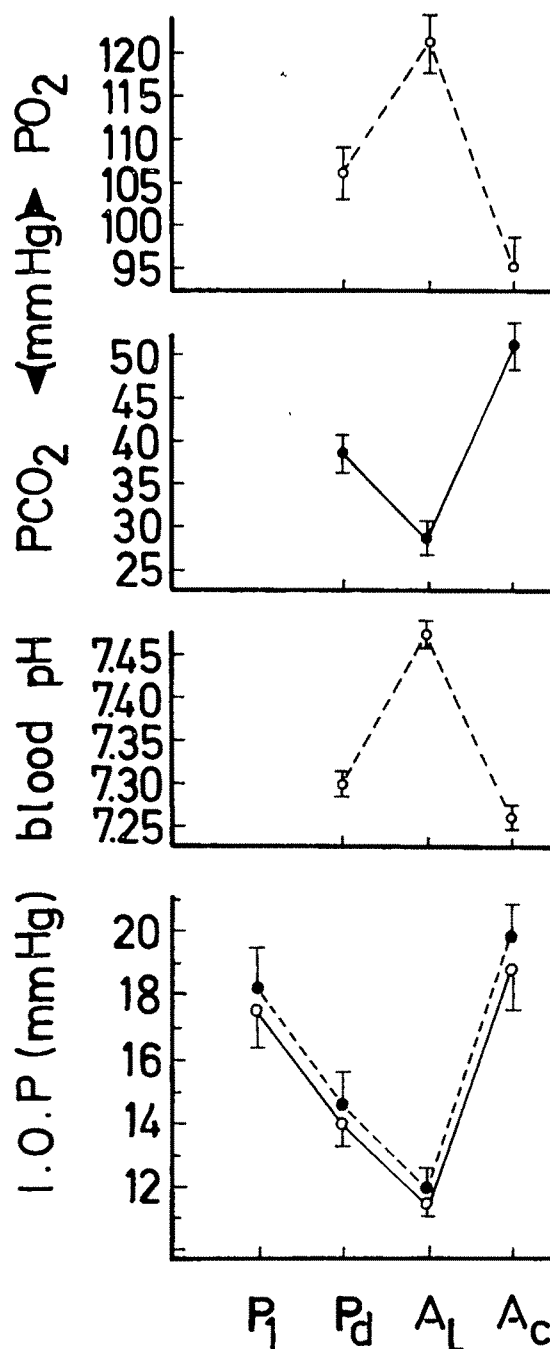


Fig. 2 Lack of effect of acetazolamide on IOP changes induced by hyperventilation and hypercapnea during general anaesthesia (number of observations = 10; vertical bars = SD of the mean). P_1 = IOP values before acetazolamide administration. P_d = IOP values 1 hour after acetazolamide administration orally and immediately after induction of anaesthesia. A_L = Hyperventilation, alkalosis (roughly 1 1/2 hour after induction). A_C = Hypercapnea, acidosis (approximately 1 hour after induction of anaesthesia and usually near recovery time).

to increased PCO_2 . The difficulties in explaining our results were due to the mechanism whereby acetazolamide reduces intraocular pressure, which is not entirely clear.

One theory is that part at least of the decrease in IOP which occurs after acetazolamide administration is explained by an induced systemic acidosis.^{7,8} Others^{12,13} seem to favour a vascular theory, suggesting that the mechanism of reduced aqueous formation may be due to vasoconstriction in afferent ciliary processes, decreasing ultrafiltration. Neither theory accounts for the inhibition of carbonic anhydrase. Inhibition of this enzyme, resulting in inhibition of bicarbonate formation, appears to be the basic explanation of the reduced secretion of aqueous humour.¹⁴

In our experiments according to the vasoconstrictive theory the pretreatment with acetazolamide should prevent the uveal vasodilation induced by increased PCO_2 , but no antagonism was observed. Moreover, the systemic acidosis induced by acetazolamide administration was uncompensated, because pulmonary hyperventilation was mechanically prevented (manual control of ventilation), and so the increased CO_2 was not removed. This should result in potentiation of the IOP-decreasing effect of acetazolamide and not its abolition. As a matter of fact the most suitable explanation is that the increased venous pressure, as well as the uveal vasodilation, induced by increased PCO_2 and not affected by acetazolamide (at least in the administered doses), were capable of reversing the IOP-decreasing effect of acetazolamide. Evidently more elaborate experiments in animals are required to clarify the role of acetazolamide in IOP changes induced by PCO_2 alterations.

We believe that our results have clinical value. This is in the determination of intraocular pressure in children, which always requires general anaesthesia. Probably the intraocular pressure which is measured without determination of PCO_2 is rather inaccurate whatever the anaesthetic agent used. Also, there is a problem in patients undergoing intraocular surgical procedures such as cataract extraction under local anaesthesia. These patients

are always hypoventilated because of the grossly limited breathing space due to the covering of their face. Sometimes the harmful and (inexplicable) elevation of intraocular pressure during the critical time of the operation is due to increased PCO_2 , and according to our results (and to our experience in 4 cases) the routine preoperative administration of acetazolamide does not prevent this result.

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The effect of autonomic agents on the pupil and the intraocular pressure of eyes treated with dexamethasone

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SUMMARY In an attempt to determine the presence or absence of correlation between the intraocular pressure-increasing and pupil-dilating effects of corticosteroids, the effect of topically applied dexamethasone and various autonomic agents has been studied in 12 hospitalised, healthy, young adult volunteers. Dexamethasone caused an average increase of intraocular pressure of 8.8 mmHg and of pupillary diameter of 0.36 mmHg; there was no significant correlation between the change in pressure and the change in pupil size. Furthermore, there was no correlation between magnitude of rise of intraocular pressure and miotic effect of methacholine 2.5%, or mydriatic effect of epinephrine 0.1%, or norepinephrine 0.1%. Dexamethasone-treated eyes showed a greater decrease in pupillary diameter in response to methacholine than their untreated mates (-1.14 and -0.68 mm respectively) and a slightly smaller increase in response to epinephrine than their controls (-0.18 and -0.53 respectively). Methacholine caused an increase in intraocular pressure of 2.8 mmHg in control eyes and 6.0 mmHg in dexamethasone-treated eyes. Increases of less significance were caused by epinephrine and norepinephrine. Subjects with the largest rise of intraocular pressure in response to dexamethasone also showed the greatest increase in intraocular pressure in response to the autonomic agents and to the water drinking test. Furthermore, they had lower coefficients of aqueous outflow than those having smaller responses. Methacholine 2.5% produced miosis in over 50% of normal control eyes.

Dilatation of the pupil occurs in many individuals receiving topical corticosteroids.¹ An increase of intraocular pressure has also been noted in many of them, but there does not appear to be a correlation between dilatation of the pupil and rise in pressure.²⁻⁴

The purpose of the present study was to attempt to determine if sensitivity to agents of the sympathetic or parasympathetic nervous system (1) accounts for the pupillary dilatation or (2) plays a role in the increase of intraocular pressure seen in corticosteroid-treated patients.

Materials and methods

Twelve normal college students ranging in age from 17 to 21 were studied. They were admitted to hospital for the entire duration of the study. The

sexes were equally represented. Medical histories were unremarkable; none had signs or symptoms of glaucoma and none knew of any member of his family who had glaucoma. General physical and ocular examinations were normal.

Before administration of any medication intraocular pressures were determined by Goldmann applanation tonometry daily at 7 to 8 o'clock in the morning for at least 1 week, and tonographies were performed with the Mueller Electronic Tonometer. Each time intraocular pressure was measured pupillary diameter was estimated by utilising the scale on the Goldmann perimeter (with standard illumination and with an attempt to keep accommodation uniform).

Before and about 4 weeks after starting dexamethasone 0.1%, 5 times a day in one eye, the responsiveness of the pupil and the intraocular pressure to various autonomic nervous system drugs was tested. Epinephrine 0.1%, norepinephrine 0.1%, and methacholine 2.5% were employed. One

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drop of the medication being tested was instilled in both eyes, and pupil size and intraocular pressure were determined every 15 minutes for at least 2 hours. Subsequent measurements were made less frequently for the next 24 hours. Water drinking tests were also done before and about 4 weeks after administration of dexamethasone; tap water was drunk within 5 minutes (14 ml per kg), and intraocular pressures were determined prior to and at 10 minute intervals for one hour after drinking; all subjects were fasting.

Throughout the study intraocular pressure was measured daily and tonography performed weekly. In some subjects frequency of administration of dexamethasone was decreased when it became apparent that 5 drops a day was producing an excessive rise in intraocular pressure.

Results

Dexamethasone 0.1%, 4 or 5 times a day, produced an average increase of intraocular pressure of 8.8 mmHg (Table 1). There was no significant change in coefficient of aqueous outflow (C) (Table 1). The intraocular pressure and coefficient of aqueous outflow of the untreated eyes did not change significantly (Table 1).

Though almost all subjects had a slight increase in the size of the pupil of the dexamethasone-treated eye, this was frequently transient. Average pupil size of treated eyes was 5.20 mm and untreated eyes (4.84 mm (Table 2). There was no correlation between the increase in the size of the pupil caused by the topical dexamethasone and the concurrent rise of intraocular pressure. Ptosis and temporarily blurred vision were noted occasionally, but no serious side effects occurred.

Table 1 *Effect of dexamethasone 0.1% on intraocular pressure and coefficient of aqueous outflow in 12 normal volunteers*

	Before treatment	After 30 days of treatment	Difference, pre vs. post
Intraocular pressure (mmHg)			
Untreated eye	12.1	12.6	+0.5
Treated eye	12.2	21.0	+8.8*
Difference between eyes	0.1	8.4	8.3*
Coefficient of aqueous outflow (μl/min/mmHg)			
Untreated eye	0.27	0.24	-0.03
Treated eye	0.26	0.22	-0.04
Difference between eyes	0.01	0.02	0.01

*Statistically significant difference ($P < 0.01$).

Table 2 *Effect of autonomic agents on the pupillary diameter of eyes of normal volunteers treated with dexamethasone in 1 eye*

	Before ANS agent (mm)	After ANS agent (mm)	Change (mm)
Methacholine, 2.5%			
Control eye	4.84	4.16	-0.68**
Dexamethasone eye	5.14	4.00	-1.14*
Epinephrine, 0.1%			
Control eye	4.74	5.27	+0.53***
Dexamethasone eye	5.25	5.43	+0.18
Norepinephrine, 0.1%			
Control eye	4.93	4.85	-0.08
Dexamethasone eye	5.22	5.04	-0.18
Total			
Control eye	4.84		
Dexamethasone eye	5.20		
Difference between eyes	0.36***		

ANS=Autonomic nervous system. *Statistically significant: * $P \leq 0.01$. ** $P \leq 0.02$. *** $P \leq 0.05$.

Table 3 *Effect of autonomic agents on the intraocular pressure of eyes with dexamethasone*

	Before ANS agent (mmHg)	After ANS agent (mmHg)	Change (mmHg)	%
Methacholine, 2.5%				
Control eye	12.3	15.1	+2.8	23
Dexamethasone eye	17.9	23.9	+6.0	33
Epinephrine, 0.1%				
Control eye	11.3	12.9	+1.6	11
Dexamethasone eye	19.8	22.2	+2.4	13
Norepinephrine, 0.1%				
Control eye	11.6	12.6	+0.8	7
Dexamethasone eye	20.8	22.1	+1.3	5

ANS=Autonomic nervous system.

Administration of several of the autonomic nervous system drugs produced changes in intraocular pressure as well as in pupillary size (Tables 2 and 3). When these alterations were biphasic, both the greatest and the smallest values were recorded and averaged separately in the statistical analysis. The tables include only the predominant changes.

The miotic effect of methacholine 2.5% was small but definite. 47% of control eyes had no change in pupil size, 31% a 1 mm decrease, 19% a 2 mm decrease, and 3% a 3 mm decrease. Responsiveness was accentuated by pretreatment with

Table 4 *Effect of methacholine 2.5% on the pupil*

Amount of constriction (mm)	Control eyes (36) (%)	Dexamethasone-treated eyes (12) (%)
0	47	29
1	31	35
2	19	29
3	3	7

dexamethasone (Table 4). Epinephrine 0.1% had a greater mydriatic effect on control eyes than on those treated with dexamethasone. The magnitude of reaction was small in both groups but was statistically significant in the control eyes. Norepinephrine 0.1% appeared to be without significant effect on the pupil.

None of the untreated subjects showed an increase of intraocular pressure greater than 7 mmHg in response to an oral water load; on the other hand 50% of eyes treated with dexamethasone had rises greater than 7 mmHg.

Discussion

Greater increases of intraocular pressure in steroid-treated eyes in response to cycloplegics and to water drinking have been noted by others.⁴⁻⁶ The effects on the pupil have not, however, been extensively studied. There is some evidence that this effect is not in actuality related to the steroid itself. Newsome and coworkers have noted that mydriasis and ptosis were induced by the vehicle of dexamethasone phosphate (Decadron), but not by dexamethasone in saline.⁷ They also noted a lack of correlation between pupil and lid changes on one hand and rise in pressure on the other. Kern and Macri reported that isolated preparations of sphincter and dilator muscle from monkey eyes showed a greater responsiveness to varying agents when the bathing solution contained the vehicle of steroid drops, but not when it contained the steroid alone.⁸

The results of the present study do not explain the mechanism of dexamethasone-induced dilatation of the pupil. Specifically they do not demonstrate any increased sensitivity to agents of the sympathetic nervous system or a decreased sensitivity to cholinergic stimuli. Indeed there was an inhibition of sympathetic and facilitation of parasympathetic activity. An additional indicator of this lack of relationship between responsiveness of the pupil and sensitivity to autonomic agents is the slightly ptotic lid which is fairly characteristic of patients treated with topical corticosteroids. If

increased sensitivity to adrenergic agents were a factor, the upper lid should not be ptotic, but should be retracted owing to stimulation of Mueller's muscle. Previous investigations of the relationship between corticosteroids and the autonomic nervous system indicate that this association is a complex one.⁹⁻¹²

The greater responsiveness of the dexamethasone-treated eyes may be a factor of greater drug penetration. The corneal permeability may have been altered by the repeated administration of the steroid drops, either due to the vehicle or the steroid. Baum has shown an increased corneal thickness after topical steroid treatment.¹³

Since Scheie's report that methacholine causes pupillary constriction in patients with Adie's syndrome, it has been generally believed that methacholine 2.5% is without effect on the pupil of normal individuals.¹⁴ This was not confirmed in the present study, in which a decrease in pupil size of 2 mm or greater was noticed in almost one-quarter of the control (normal) eyes (Table 4). This responsiveness may be related to the freshness of the solution used, for methacholine is unstable in solution and in the present study was prepared immediately prior to administration.

It was of interest that eyes most sensitive to the ocular hypertensive effect of dexamethasone reacted most markedly to the other tests employed in the present study; they showed the greatest intraocular pressure response to methacholine, epinephrine, norepinephrine, and the water drinking test (Table 5). In fact the 3 groups in Table 5 behave differently

Table 5 *Effect of various autonomic agents on intraocular pressure, depending on the responsiveness of the eye to the intraocular pressure-inducing effects of dexamethasone: Each group consists of 4 normal volunteers, grouped according to the responsiveness of their intraocular pressure to dexamethasone*

	Group I	Group II	Group III
Rise in intraocular pressure (mmHg)	3.3	7.8	15.5
Response to methacholine, 2.5% (mmHg)	+5.3	+3.3	+8.2
Response to epinephrine, 0.1% (mmHg)	+2.0	+4.0	+7.8
Response to norepinephrine, 0.1% (mmHg)	+0.3	+0.5	+3.0
Response to water drinking test (mmHg)			
Before dexamethasone	+2.5	+3.0	+2.5
After dexamethasone	+3.0	+6.4	+9.7
Change in C (μ l/min/mmHg)	+0.03	+0.01	-0.05

enough from each other to indicate that each group represents a different population from the other 2. The large increase of pressure induced by methacholine is surprising, especially in view of the usual hypotensive effect of this medication. Dexamethasone-sensitive eyes showed a decrease in coefficient of aqueous outflow which the less reactive eyes did not (Table 5).

This close correlation between the ocular hypertensive effect of dexamethasone and the ocular hypertensive effect of the various autonomic agents forms an intriguing contrast to the lack of relationship between dexamethasone-induced rise in pressure and pupil size and the similar lack of relationship between rise of pressure and sensitivity to the pupillary effects of several autonomic agents. Those eyes sensitive to the intraocular pressure-inducing effect of corticosteroids were also more sensitive to other external (and perhaps internal) stimuli that effect intraocular pressure. As such these eyes may be manifesting what has classically been considered one of the characteristics of the glaucomatous eye.

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Intraocular pressure response to corticosteroids in children

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SUMMARY A total of 44 children who suffered from vernal conjunctivitis were treated with topical dexamethasone 0.1% 4 times daily for 6 weeks and tested for their intraocular pressure. There was a statistically significant difference ($P < 0.01$) between the responders in our group of children and a group of normal adults reported on by Armaly in 1965.

Topically administered corticosteroids are widely used in treating a large range of inflammatory and allergic eye conditions. But their use has been partially limited after Armaly¹ reported the increase in intraocular pressure (IOP) produced by locally instilled corticosteroids. The 'corticosteroid response' was found by Armaly¹ after subjecting a sample of normal population to topical corticosteroid instillation and monitoring the increase in their IOP. According to the increase in the IOP, 3 categories of response are distinguished in the normal adult population: low (66.2%), intermediate (28.8%), and high (5%). Furthermore, Armaly¹ found that the steroid response is hereditary.

To the best of our knowledge there are no published data on the pressure-raising effect of topically administered steroids in children from families free from glaucoma.

Materials and methods

In the present study we are reporting the influence of topically administered corticosteroids on the intraocular pressure in children treated for vernal conjunctivitis.

Forty-four children were diagnosed as suffering from this disease and needed treatment with topical steroids. There were 32 boys and 12 girls, whose ages ranged from 4 to 19 years, average of 9.7 years. None of them were treated with steroid, topically or systematically, for at least 4 weeks. The treatment was identical in all cases: Dexamethasone phosphate

Table 1 *Corticosteroid test in normal patients*

Increase in intraocular pressure mmHg		Our results (44 children)	Armaly's results (80 adults)
≤ 5 mmHg	Low responder	39 (89%)	53 (66.2%)
6-15 mmHg	Intermediate	4 (9%)	23 (28.8%)
16+ mmHg	High	1 (2%)	4 (5%)

0.1% ophthalmic solution was applied to both eyes 4 times daily for 6 weeks. The intraocular pressure was measured every 2 weeks with the Goldmann applanation tonometer. A pressure rise of up to 5 mmHg was considered a low response, 6-15 mmHg intermediate, and 16 mmHg and above high.¹ The statistical analysis was by the chi-square method.

Results

Thirty-nine children (89%) showed either no rise in IOP or a rise of less than 6.0 mmHg. Four children showed an increase of 6-15 mmHg. Only 1 child was found to have an increase in his intraocular pressure more than 16 mmHg (2%). The results are shown in Table 1.

Discussion

Comparing the results in our children with those from Armaly's normal adults (Table 1) shows the differences in the steroid response to be not significant. However, if one considers the intermediate and high responders together (5 out of 44 children (11%) and 27 out of 80 (33.8%) adults) this difference is statistically significant ($P < 0.01$). In other

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words, our results indicate that the hypertensive response to steroid instillation in our sample of children is lower than in normal adults. In children of parents suffering from glaucoma Francois³ reported 34% positive responders (intermediate and high).

It should be noted that the average initial IOP found in our children was 11.2 ± 2.0 , which is below the accepted normal IOP in adults 16.0 ± 3.0 .⁴ This finding might explain the lower steroid response in children than in normal adults, as a higher initial IOP is expected later in life. This may produce an increase in the steroid responsiveness also.

Although these 3 groups were differentiated on the basis of the magnitude of pressure rise, the time of pressure rise was also different, and it is of clinical significance. Group 1, the low responders, showed a slight pressure rise at the end of 2 weeks, and the pressure remained stabilised afterwards. In groups 2 and 3 (11%) the pressure rose continuously with further treatment. The clinical implication of this is that a child who has received topical corti-

costeroid treatment for a month but still has pressures below 21 mmHg is unlikely to have a further increase in his or her intraocular pressure. Should the pressure be above 21 mmHg at the end of the first month, subsequent steroid therapy should include careful monitoring of the intraocular pressure.

These results do not differ substantially from previously reported observations on time-dependent IOP raised in normal adults.¹

We thank Mrs Bilha Savell for her technical assistance.

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Characteristics of reduction of intraocular pressure after trabeculectomy

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SUMMARY The change in intraocular pressure achieved after 98 trabeculectomy operations performed on 70 patients with primary open-angle glaucoma was analysed. The reduction was proportional to the untreated preoperative pressure, and the results indicated that a first trabeculectomy reduced the intraocular pressure to between 16 and 20 mmHg irrespective of its initial level. Cases which required medical therapy for final pressure control after surgery showed a distribution of initial intraocular pressure similar to those not requiring such therapy. In addition, these cases were reduced to a level of pressure only slightly above the arbitrary figure of 20 mmHg before medical therapy was added, and were therefore considered almost to have reached the normal physiological range. Cases submitted to a second trabeculectomy are discussed, including 2 cases with unexplained acute open-angle glaucoma some months after the first operation.

Trabeculectomy has gained worldwide acceptance as perhaps the safest and most effective drainage operation for glaucoma. While the pressure reducing effect is comparable to that of other drainage procedures, it has been shown to have a lower risk of delayed reformation of the anterior chamber, cataract, and ruptured or infected drainage bleb.¹⁻⁷ None of these authors has, however, determined whether or not the eyes with the highest pressure before treatment are the most likely to require supplementary treatment after trabeculectomy. In 1975 Watson and Barnett⁸ did state that another operation produced the same absolute reduction in intraocular pressure as the first operation, but Watson (personal communication) has recently revised this opinion.

This paper examines the characteristics of the intraocular pressure reduction following trabeculectomy in primary open-angle glaucoma to determine whether or not it is possible to predict the level of pressure after surgery.

Material and methods

A retrospective analysis of the reduction of intraocular pressure achieved by trabeculectomy was performed on 98 eyes (70 patients). All cases were first operations for primary open-angle glaucoma, including pseudoexfoliation (3 eyes), developmental

(10 eyes), pigmentary (2 eyes), and low-tension glaucoma (2 eyes). Cases of angle closure or secondary glaucoma were excluded to avoid the possibility of distortion of the level of preoperative intraocular pressure by transient factors. Similarly we excluded cases of uncertain diagnosis and those with unreliable applanation recordings.

Operative technique followed the description by Watson,^{9,10} and the procedures were carried out by various members of the junior and senior surgical staff. Eyes with postoperative hyphaema or shallow anterior chamber were included, but 1 case with iris incarcerated in the trabeculectomy fistula was rejected.

Applanation pressures (Goldmann) were recorded at the time of initial diagnosis or in the immediate preoperative period if the patient was not then using medical therapy to reduce the intraocular pressure. Most cases required operation within 1 year of diagnosis, but cases with no record of untreated pressure in the 2 years prior to surgery were excluded. After operation pressures in those eyes not requiring medical therapy were recorded at 1 and 3 months after surgery and at the time of latest follow-up, which ranged from 9 months to 5½ years. Where several applanation recordings were available for 1 assessment period, the highest was used for analysis. Similarly the highest peaks of intraocular pressure fluctuation were used when assessing the need for additional therapy after operation.

Regression equations were determined for the relationship of initial pressure to pressure reduction

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at both 3 months and final follow-up. The statistical probability of these being straight-line relationships was assessed by calculation of the regression coefficient (r), and the difference between the two graphs was tested by Fisher's transformation. The results were calculated for every eye in the series but were also checked by using only one eye selected at random from those patients having operations on both eyes.

Eyes which required further medical or surgical measures to maintain the intraocular pressure below 20 mmHg after operation were studied separately to determine whether or not their exclusion from the main analysis might significantly alter the results, and to this end their initial pressures were compared with those of the whole group. Eight of these eyes underwent a second trabeculectomy within the time of follow-up, and the effect of this subsequent procedure on the intraocular pressure was noted.

Results

EFFECT OF A FIRST TRABECULECTOMY

The reduction of intraocular pressure after a first trabeculectomy was plotted against the initial or

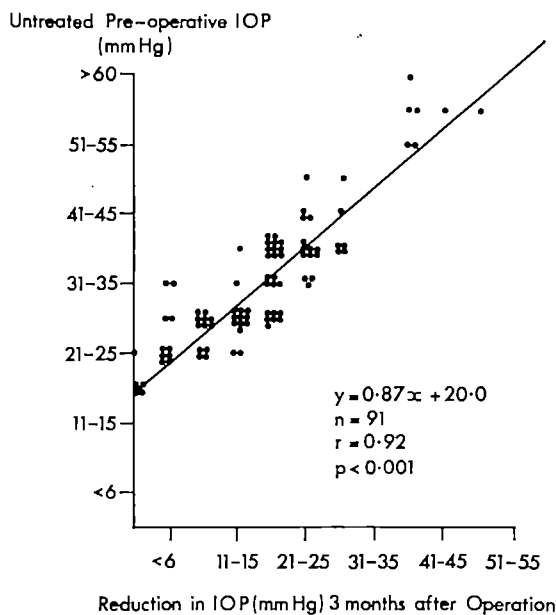


Fig. 1 The effect of a first trabeculectomy on the intraocular pressure (IOP) 3 months after operation in primary open-angle glaucoma. The reduction in pressure is proportionate to the initial pressure and is likely to restore the pressure to the physiological range (n =number of eyes, r =regression coefficient).

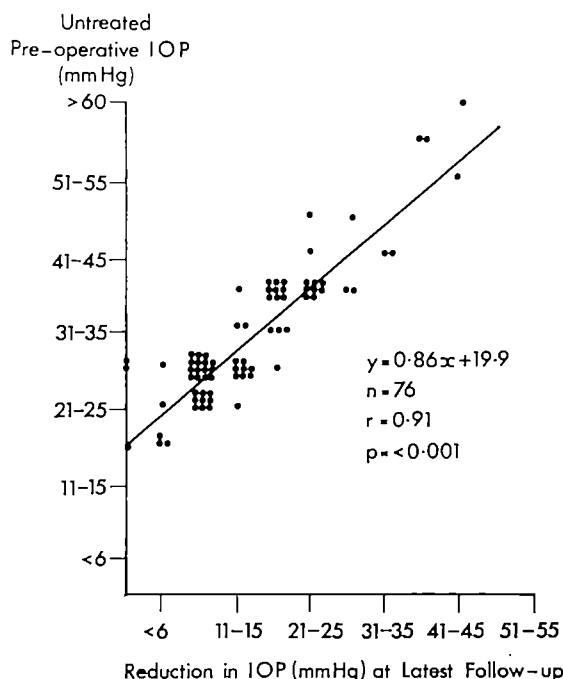
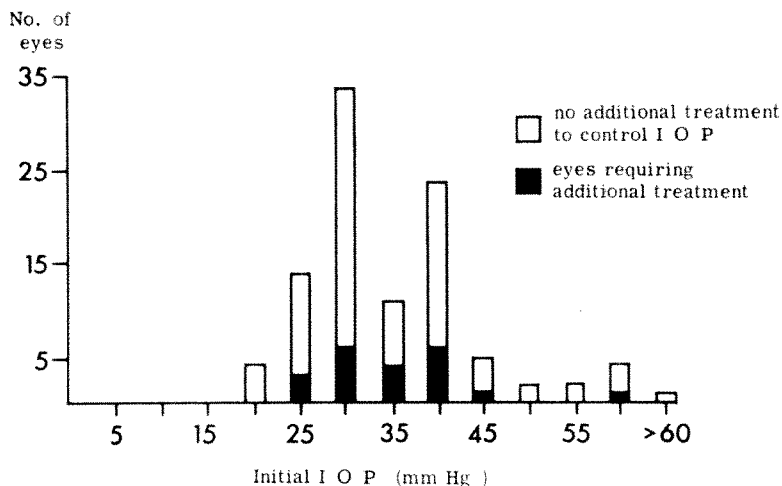


Fig. 2 The effect of a first trabeculectomy on the intraocular pressure at latest follow-up, minimum 9 months, maximum 5½ years. The relationship is similar to that in Fig. 1 (Fisher's transformation).

untreated pressure for each eye, and the results at 3 months after operation are displayed in Fig. 1. For initial pressures between 16 and 60 mmHg the drop in pressure was found to be directly proportional to the initial level, and the relationship could be expressed by the equation $y = 0.87x + 20.0$ ($n = 91$, $r = 0.92$). The level of significance, $P < 0.001$, is high enough to confirm that the results represent a true straight-line correlation. Fig. 2 shows the same analysis using the drop in pressure at the time of latest follow-up and is a straight line of similar significance, $y = 0.86x + 19.9$ ($n = 76$, $r = 0.91$, $P < 0.001$). In both figures the line cuts the ordinate between 16 and 20 mmHg. The results were identical when only 1 eye from each patient was used in the analysis.

Fig. 3 is a histogram comparing the distribution of initial pressures of eyes requiring further medical or surgical treatment to the distribution of initial pressures of the population displayed in Figs. 1 and 2. As there were only 6 such cases at the 3-month assessment, the histogram shows the total number of 22 cases on supplementary treatment at final follow-up. Inspection indicates that these eyes are evenly distributed throughout the whole series and

Fig. 3 Histogram showing the similar distribution of initial pressures of eyes requiring supplementary therapy after trabeculectomy (shaded), compared with the distribution in eyes controlled below 20 mmHg without supplementary medical therapy (unshaded).



do not come from a separate group with high initial pressures. The mean pressure at which supplementary postoperative therapy was introduced for various clinical reasons was 25 mmHg (range 21–32 mmHg).

EFFECT OF REPEAT TRABECULECTOMY

Eight eyes (6 patients) had a second trabeculectomy carried out within the period of the study. One of these eyes had pigmentary glaucoma and is described below, but the others had primary open-angle glaucoma without pseudoexfoliation or developmental anomaly. In 6 eyes there had been immediate residual hypertension not controlled to a level below 20 mmHg with medical agents, and in these cases the additional hypotensive effect of the second operation was small, all still requiring supplementary medical therapy. In the other 2 cases there had been good control for several months after the first operation, followed by sudden inexplicable extreme rise of pressure. Both these cases were stabilised by a second operation, and as they seem to have behaved similarly in producing delayed acute glaucoma with open angles they will be described in detail.

Case 1. A 58-year-old woman had uncomplicated trabeculectomy operations on each eye because of pigmentary glaucoma not controlled on maximum medical therapy. The initial pressure was 38 mmHg right eye, 42 mmHg left eye. There was deep cupping of the left optic disc and early arcuate scotomata in the fields of both eyes. Postoperative applanation pressures were, approximately, 12 mmHg right eye, 8 mmHg left eye on numerous occasions up to 6 months after surgery. The patient presented 9 months after operation with blurring of vision in the left eye of 24 hours' duration followed by haloes, severe frontal headache, and vomiting.

There was acute congestion of the globe with corneal oedema. The pressure was approximately 80 mmHg by applanation but the anterior chamber was of normal depth and the pupil was reactive. Gonioscopy after clearing the cornea with glycerol revealed an open angle with pigmentation as before, a patent peripheral iridectomy, and a trabeculectomy site with diffuse drainage bleb. There was no aqueous flare, cells, or pigment particles. A further trabeculectomy was performed a few days later with control between 10 and 15 mmHg over the following 3½ years. The right eye has had an uneventful course, with pressure between 10 and 14 mmHg over 4 years.

Case 2. A 53-year-old woman with primary open-angle glaucoma with early optic disc cupping and early visual field defects had uncomplicated trabeculectomies in both eyes because of intolerance of medical treatments. The untreated initial intraocular pressures were 26 mmHg right eye, 25 mmHg left eye. After surgery the pressures were controlled at approximately 15 mmHg right eye, and 5 mmHg left eye for 10 weeks, but 1 week later she reported with a history of 48 hours of severe pain and blurring of vision in the left eye, which showed typical signs of acute glaucoma but with a deep and quiet anterior chamber and a normally reactive pupil. The intraocular pressure was over 60 mmHg. Gonioscopy confirmed a wide open drainage angle and patent peripheral iridectomy with unobstructed trabeculectomy site and undisturbed drainage bleb. Trabeculectomy was repeated adjacent to the site of the first operation, and for the succeeding 2 years the pressure has been between 6 and 18 mmHg without additional therapy. The pressure in the right eye has remained between 10 and 15 mmHg without supplementary therapy since the first operation.

Discussion

This study is of a group of cases with specified type and duration of glaucoma selected to allow clear assessment of the pressure changes achieved by trabeculectomy and to avoid sources of error such as drug therapy or transient increases in preoperative pressures. As eyes with a postoperative pressure of over 20 mmHg were excluded from Figs. 1 and 2 because of the introduction of supplementary medical therapy, it is essential to demonstrate that this group does not differ from the overall population and that its exclusion from the results does not introduce an unacceptable error. These cases represent only 6.2% at 3 months and 22.5% at final follow-up, and it has been shown in Fig. 3 that they have a distribution of initial pressures similar to the eyes included in the graphs in Figs. 1 and 2. Thus they do not form a separate group with initial pressures higher or lower than the more successful cases. It is also useful to consider the level of intraocular pressure at which supplementary medical treatment was introduced, and the mean of 25 mmHg confirms that most of the eyes excluded from Figs. 1 and 2 achieved a valuable reduction of pressure to near normal values. The straight line demonstrated may therefore be accepted as the expression of pressure reduction after a first trabeculectomy in primary open-angle glaucoma.

The slope of the line in both Figures cuts the ordinate at 16–20 mmHg, indicating that for values of preoperative intraocular pressure from 16 to 60 mmHg the effect of a first operation is to reduce the pressure to within the range of physiological normal. The slight difference between the straight lines in Figs. 1 and 2 is not significant (Fisher's transformation).

Consideration of those few cases submitted to repeat trabeculectomy suggested that, if there had been no technical reason for failure, little extra hypotensive effect was gained unless there had been a recurrence of hypertension after a period of satisfactory control. The cause of the acute rise in intraocular pressure in the 2 cases described remains unexplained.

It is interesting to speculate on why the operation seems to restore the intraocular pressure to the physiological range despite a wide variation in initial pressure. This phenomenon might be used to gain an understanding of the control mechanism regulating the intraocular pressure, but we have not been able to form a hypothesis, partly because of uncertainty about the cross-sectional area and resistance of the fistula in a series of cases operated upon by several surgeons, whose operations may have slightly differing dimensions. Nevertheless the apparent constant effect of a single fistula merits further study.

These results should not be considered evidence for rejecting trabeculectomy in the management of low-tension glaucoma. The number of cases in this study with initial intraocular pressure below 20 mmHg is very small and does not allow accurate extrapolation of the graph into the low-tension range. Moreover we know little of the role of transient and undetected pressure elevations in the loss of visual field in this condition.

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Trabeculectomy: a review and 4-year follow-up

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SUMMARY Since the first attempt at glaucoma surgery in 1830 many surgical procedures have been devised and adopted depending on the understanding of the aetiology and pathogenesis of the disease. Trabeculectomy, the most recent drainage procedure for glaucoma, has become a widely used, effective, and safe method, particularly for chronic simple glaucoma. Up to 4 years' follow-up of 66 eyes (55 patients) is reported. The findings at 6 months, 1 year, 2 years, 3 years, and 4 years were in agreement with previous reports by other authors. The main postoperative complication was transient hyphaema. Of the total number of eyes, 7 needed miotic drops and 5 required further surgical procedures to control the intraocular pressure.

Since Cairns described trabeculectomy,¹ it has been adopted by many ophthalmic surgeons, as it is a relatively effective and safe drainage procedure, particularly for chronic simple glaucoma.

The previously described drainage procedures of anterior sclerotomy, partial sclerotomy and iridectomy, cyclodialysis, iridencleisis, corneoscleral trephine and iridectomy, and sclerocautery have all been found to be unsatisfactory for some reason or other, among which the following are the commonest.

(1) *Loss of anterior chamber.* The anterior chamber was lost or became very shallow during surgery or postoperatively, with resulting complications such as anterior synechiae formation, secondary glaucoma, and cataract.

(2) *Infection.* Owing to the superficial situation of the bleb (being covered only by the conjunctiva and Tenon's capsule) infection was the most feared complication. Some eyes were lost as a result of intraocular spread of the infection, resulting in panophthalmitis.

(3) *Large bleb.* In some eyes the bleb became so large that it not only became cosmetically embarrassing but also covered the cornea and the pupil, causing visual disturbance.

(4) *Malignant glaucoma.* Some eyes developed malignant glaucoma soon after surgery. This was due to the forward displacement of the vitreous and the iris-lens diaphragm obstructing the pupil and the outflow of the aqueous humour.

(5) *Closure of the fistula.* This was the main long-term complication and occurred as a result of subconjunctival fibrosis. This is commonest in Africans.²

Because no operation was free of complications the attention of researchers was directed at the trabecular meshwork where the obstruction to outflow was thought to lie. Thus Redmond Smith described trabeculotomy³ and was followed by Allen and Burian⁴, and Harms and Dannheim.⁵ Krasnov described sinusotomy⁶ and finally Cairns described trabeculectomy.¹ Cairns's original method was modified by Watson⁷ and has since then been adopted by many ophthalmic surgeons with a few minor surgical modifications. Most authors agree that the mechanism of drainage following trabeculectomy is by the formation of a fistula between the anterior chamber and the subconjunctival space.

Several reports have described the results of trabeculectomy, which are promising in the control of raised intraocular pressure and have few complications. Thus Thyer and Wilson⁸ reported encouraging results, and Ridgway *et al.*⁹ reported a success rate of 92%. Ridgway¹⁰ reported further successes with this operation.

Negroes respond poorly to filtering surgical procedures. Welsh² concluded that failure of fistula formation is due mainly to overgrowth of the external scleral fistula by fibrous tissue derived from the sclera and Tenon's capsule. But with trabeculectomy Welsh¹¹ reported a success rate of 65% in Negroes and Freedman *et al.*¹² 86% in black Americans.

Tord Jerndal and Viiru Kriisa¹³ reported control of intraocular pressure in 42 out of 52 cases (80.76%)

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Table 1 Pre- and post-operative intraocular pressure in mmHg

Level of IOP	No. of eyes						
	Before op.		After op.				
		1/12	6/12	1 year	2 years	3 years	4 years
<21	0	56	54	46	45	37	16
21-30	44	7	8	9	5	3	4
31-40	18	2	4	2	0	1	
41-50	3	1	0	0	1	1	
51-60	1	0	0	0	0	0	
Total	66	66	66	57	51	42	20

Age range: 20-83 years. Mean age: 50 years.

of pseudoexfoliative glaucoma. Sandford Smith¹⁴ came to the conclusion that trabeculectomy produced fewer complications but otherwise there was little difference in the control of intraocular pressure. A few cases of combined trabeculectomy and cataract extractions have been reported, but without any conclusive results as the cases are too few.⁸

The purpose of this paper is to report the follow-up of 66 eyes (55 patients) up to 4 years after trabeculectomy for uncontrolled chronic simple glaucoma, except for 3 eyes, 1 with chronic closed-angle glaucoma and 2 with neovascular glaucoma (central retinal vein occlusion).

Material and methods

Trabeculectomy was performed on 66 eyes (55 patients) between the end of 1973 and the end of 1977 in 1 unit of the Manchester Royal Eye Hospital. All the eyes except 3 showed chronic simple glaucoma; 2 had neovascular glaucoma (following central retinal vein occlusion), and 1 was a case of chronic closed-angle glaucoma.

All 66 eyes showed progressive field loss despite maximum medical treatment with local and systemic therapy—pilocarpine 4% 4 times a day, adrenaline

1% twice a day where indicated, and acetazolamide 250 mg orally 4 times a day. The presence or absence of lens opacities was noted preoperatively to determine the number of eyes developing lens opacities as a result of trabeculectomy. Fourteen eyes had lens opacities before surgery. The ages of the patients varied from 18 to 83 years, mean 50 (Table 1). The total number of patients shown is 55 and not 66 because 11 had trabeculectomy on both eyes.

The criteria for operation were progression of field defect and raised intraocular pressure above 21 mmHg despite maximum medical treatment. Patients for operation were admitted to the ward for glaucoma assessment 1 week prior to surgery. This was to ascertain that the intraocular pressure remained raised above 21 mmHg despite instillation of drops and administration of tablets by trained staff.

Intraocular pressures were recorded twice a day by applanation tonometry. The immediate pre-operative intraocular pressures were recorded and divided into 4 groups (Table 1): (1) 21-30 mmHg, (2) 31-40 mmHg, (3) 41-50 mmHg, (4) 51-60 mmHg. Visual acuity (Snellen's chart) was also recorded before surgery and the patients were divided into 3 groups (Table 2): (1) 6/4-6/12, (2) 6/18-6/60, (3) Less than 6/60. Intraocular pressures and visual acuity were recorded at 1 month, 6 months, 1 year, 2 years, 3 years, and 4 years after the operation and compared with the preoperative findings (Tables 1 and 2). Any lens opacities were also recorded. Immediate and late complications were noted.

It will be noticed from Tables 2 and 3 that from the sixth month the end of the 4 years the total number of eyes becomes less. This is because the study began in 1973 and cases are recorded from then until the end of 1977, so not all eyes were subjected to the 4-year follow-up.

SURGICAL TECHNIQUE

Most operations were carried out under a local anaesthetic by the consultant or senior registrar,

Table 2 Pre- and post-operative visual acuity (Snellen's chart)

Visual acuity	No. of eyes and percentage									
	Before op.		After op.							
	No. of eyes	(%)	No. of eyes	(%)	No. of eyes	(%)	No. of eyes	(%)	No. of eyes	(%)
6/4-6/12	36	(54.5)	26	(39.3)	22	(36.5)	17	(33.3)	14	(33.3)
6/18-6/60	16	(24.25)	27	(41)	20	(35.0)	18	(35.2)	13	(30.9)
Less than 6/60	14	(21.25)	13	(19.6)	15	(26.3)	16	(31.3)	15	(35.9)

Table 3 Percentage of eyes with intraocular pressure less than 21 mmHg after surgery

Postoperative duration	No. of eyes with IOP <21 mmHg	Total eyes	%
One month	56	66	84.4
Six months	54	66	81.8
One year	46	57	80.7
Two years	45	51	88.1
Three years	37	42	88.9
Four years	16	20	80.0

except on 2 eyes which were operated on by the registrar. Promethazine 25 mg was given intramuscularly as premedication 1½ hours before surgery to the patients to be operated on under a local anaesthetic. All eyes were operated on with the aid of a surgical microscope.

A 6–7 mm limbal based conjunctival flap was turned down over the cornea and the limbus was cleared of Tenon's capsule. A lamellar scleral trapdoor 4 mm wide and extending 5 mm posteriorly from the limbus was dissected forwards to hinge anteriorly at the 12 o'clock position at the limbus. The bed of this trapdoor now consists of the deep sclerotrabeular lamella, and a 4×2 mm rectangle of this lamella was marked with a razor blade fragment, the posterior incision being made along the line of the scleral spur. The sides of this rectangle were carefully deepened until penetration occurred. The rectangle of tissue was seized with fine-toothed forceps and was excised by Vanna's scissors or by razor blade fragment. A peripheral iridectomy was performed at this stage. The scleral trapdoor was closed with two 8/0 virgin silk sutures at the posterior corners. The conjunctival flap was sutured with continuous 6/0 catgut.

Atropine drops and chloramphenicol ointment were instilled and the eye was padded. The same medication was used twice a day postoperatively. All eyes were dressed 24 hours later and the patients were allowed out of bed. All patients were observed postoperatively as inpatients and were discharged after a minimum of 7 days provided there were no postoperative complications.

Results

INTRAOCULAR PRESSURE

Six months after surgery the intraocular pressure was found to be less than 21 mmHg in 54 eyes (81.8%) (Table 1). Seven eyes needed pilocarpine 4% 4 times a day to bring the intraocular pressure to below 21 mmHg. The remaining 5 eyes showed an intraocular pressure of above 22 mmHg despite

medical treatment and had to have other surgical procedures to reduce the intraocular pressure below 21 mmHg.

From Table 3 it can be seen that an intraocular pressure of less than 21 mmHg was achieved in 84.4% of eyes after 1 month, 81.8% after 6 months, 80.7% after 1 year, 88.1% after 2 years, 88.9% after 3 years, and 80.0% after 4 years.

VISUAL ACUITY

Table 2 shows that the visual acuity gradually worsened after trabeculectomy. Thus 54.5% of eyes had visual acuity of 6/4–6/12 prior to trabeculectomy, but 4 years later only 25% of eyes retained this visual acuity. Similarly, visual acuity of 6/18–6/6 was found in 35% of eyes 4 years after surgery as compared to that in 24.25% of eyes preoperatively. Before trabeculectomy the percentage of eyes with a visual acuity of less than 6/60 was 21.25%, but this had increased to 40% 4 years after surgery.

COMPLICATIONS

Immediate. Hyphaema occurred in 35 eyes (53%). Its duration varied from 1 to 21 days with an average of 7.4 days. It did not require any special treatment except rest in bed. Shallow anterior chamber was found in 7 eyes (11.6%) lasting from 2–13 days with an average of 5.57 days. Treatment with a firm pad and bandage was found to be sufficient for the reformation of the anterior chamber. Anterior uveitis with secondary glaucoma occurred in 3 eyes (4.5%) and was controlled by topical mydriatics, steroids, and acetazolamide orally. The anterior uveitis settled within 2–10 days with an average of 4 days, and with it the glaucoma.

Late. Lens opacities: Cataract was found in 6 eyes (9.8%) after 6 months. These were in addition to the eyes which had cataract prior to surgery. One eye developed central retinal vein occlusion with marked drop in visual acuity. Retinal detachment occurred in 1 eye and was treated by conventional methods without success.

Discussion

INTRAOCULAR PRESSURE

After trabeculectomy 54 eyes showed intraocular pressures of less than 21 mmHg after 1 month and were considered to be a complete success. In 7 eyes only a partial success could be claimed because the intraocular pressure of less than 21 mmHg was not achieved with trabeculectomy alone but was obtained with miotic drops, pilocarpine 4%. The remaining 5 eyes were complete failures, as they showed an intraocular pressure of more than 21 mmHg despite medical therapy. In these eyes other

surgical procedures such as cyclodialysis, Scheie's operation, and cyclocryotherapy were carried out to reduce the intraocular pressure to an acceptable level.

VISUAL ACUITY

The major cause of gradual deterioration of visual acuity was cataract. Fourteen eyes had cataracts before they underwent trabeculectomy, while 6 eyes developed cataract postoperatively. Among the other causes were central retinal vein occlusion (2 eyes had CRVO before and 1 after the surgery), retinal detachment, and the glaucoma itself in uncontrolled eyes.

COMPLICATIONS

The major complication was hyphaema, which is not surprising considering the size of the wound. A significant finding was that out of the 15 eyes which showed intraocular pressure of more than 15 mmHg after trabeculectomy 8 had postoperative hyphaema of more than 5 days' duration. It seems a fair deduction that organisation of the hyphaema may have contributed to the closure of the fistula. Immediately after trabeculectomy 10 eyes had shallow anterior chambers. This was due to excessive drainage as evidenced by large blebs.

In 6 eyes lens opacities progressed rapidly as a result of operation, with immediate reduction in visual acuity. However, visual acuity was improved with glasses in the majority of cases, while 1 patient had cataract extraction at a later date without disturbing the bleb, with reasonable improvement in visual acuity with aphakic correction. It was felt that central retinal vein occlusion and detached retina following trabeculectomy were coincidental rather than the result of the operation.

Conclusions

Trabeculectomy was an effective means of lowering the intraocular pressure to less than 21 mmHg in

80.7% of the eyes being studied. The reduction in visual acuity following trabeculectomy was due to lens opacities. In those cases which were 'operative failures' a postoperative hyphaema was present for 5 days in 50%, and it seems likely that organisation of the hyphaema blocked the fistula.

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Epithelial cyst of the iris following penetrating keratoplasty

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SUMMARY In a 35-year-old patient with keratoconus a cyst of the iris was first observed 22 months after routine penetrating keratoplasty. The lesion was completely excised and shown by light and transmission electron microscopy to be composed of conjunctival epithelium organised as a single large cyst containing serous material and occasional free epithelial cells. The management of epithelial implantation cysts is discussed. When indicated, complete surgical excision without rupture is preferred to avoid possible intraocular dissemination of viable epithelial cells that might result in further complications.

Aberrant epithelium in the ocular anterior chamber is a well recognised complication of accidental and surgical perforating wounds of the cornea. Epithelialisation involving the iris may develop as (1) solid (pearl) tumours, (2) serous cysts, (3) epithelial implantation membranes, or (4) epithelial ingrowth.^{1,2} Although each type of epithelial invasion shows different growth characteristics, all have a potential for progression, which in some cases can be rapid and extensive, resulting in visual obstruction, iridocyclitis, secondary glaucoma, and potential loss of the eye.^{1,2} The decision to intervene surgically is predicated on documented progression of the lesion and knowledge of its potential dangers. The preferred method of treatment must be based on the site affected and anticipation of the behaviour of the lesion.

We observed the occurrence and progression of a cystic lesion of the iris following penetrating keratoplasty. Treatment by excision provided the first histopathological specimen to be examined by transmission electron microscopy.

Case report

A 35-year-old Caucasian male required penetrating keratoplasty for keratoconus. His eye was otherwise normal. Penetrating keratoplasty was performed on the left eye without apparent complication, with continuous 10-0 nylon suture placed at midstromal

depth. A routine follow-up 15 months after surgery showed a clear graft, visual acuity corrected to 20/20 (6/6) with spectacles, and no abnormalities. The continuous nylon suture was removed uneventfully during the 22nd postoperative month, at which time a translucent cystic elevation of the iris about 2.5 mm in diameter was noted at the 3 o'clock position underlying the keratoplasty wound without corneal touch (Fig. 1). The pupil was slightly elliptical, but no extension of the lesion into the angle was apparent.

During a 3-month interval progression in size to about 4 mm was documented, and during the 25th month after keratoplasty the lesion was excised. A fornix-based conjunctival flap was dissected temporally. An incision was made at the limbus and extended with scissors from 2 to 4 o'clock. To avoid rupture of the cyst within the eye a Weck-cel sponge was applied to the cyst for traction, and the cyst was withdrawn from the anterior chamber. Radial section of the iris above and below the lesion was made from the angle to the pupillary margin, the base of the iris was transected, and the cyst was removed intact. The entire specimen was immediately fixed in 4% glutaraldehyde (cacodylate-buffered) and prepared for transmission electron microscopy by standard techniques.

Postoperatively the graft has remained clear with visual acuity correctable to 20/20 (6/6). Corneal astigmatism of approximately 6 dioptres before excision was reduced to 2.75 dioptres after the operation. Although we were concerned that the large temporal iridectomy might produce glare

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Fig. 1 Appearance of thin-walled iris cyst 22 months after penetrating keratoplasty. Surgical wound margin between donor and recipient corneas is apparent.

symptoms, the patient has not experienced such problems. There has been no sign of inflammation, glaucoma, or recurrent anterior chamber epithelialisation during the past 36 months.

PATHOLOGICAL FINDINGS

Gross examination. The excised iris specimen contained a thin-walled cystic structure, measuring 3.0 mm in diameter, which transilluminated easily.

Light microscopy. A solitary cyst lined by non-keratinised stratified squamous epithelium of variable thickness was almost completely embedded within the iris stroma (Fig. 2). Nasally and temporally the cyst appeared to dissect between the layers of stroma. Only a very thin layer of stroma was present between the cyst and the intact but attenuated dilator muscle and pigment epithelium of the iris. The epithelial lining was thicker nasally, temporally, and posteriorly, where it attained up to 10 cell layers (Fig. 3 inset). The epithelium was thinnest anteriorly, as was the extremely diaphanous iris stroma covering it. Nasally a nodule of the acanthotic epithelium showed desquamation of its surface cells (Fig. 4 inset). The contents of the cyst appeared almost entirely serous, although an occasional rounded-up, desquamated epithelial cell was also apparent.

Electron microscopy. Survey of the posterior aspect of the cyst revealed 4 to 5 layers of stratified epithelial cells with occasional melanocytes interspersed among the basal cell layer (Fig. 3). The iris stroma, dilator muscle, and pigment epithelium appeared ultrastructurally unremarkable. The basal epithelial cells possessed a thin, discontinuous

basement membrane with relatively few hemidesmosomal attachments. Cells of all epithelial layers contained numerous tonofilaments and several small melanosomes. The superficial cells showed innumerable microvillous projections of their free surface plasma membrane (Fig. 3 inset). Fine filamentous material, similar to the glycoprotein normally adherent to ocular surface epithelial cells, invested the surface of the microvilli. On the basis of these several ultrastructural criteria this epithelium could be judged to have originated from the limbus or bulbar conjunctiva.

Of particular interest was the nodular area of desquamating epithelial cells. Several apparently free-floating cells could be examined, and all appeared entirely viable, as they had intact plasma membranes and cytoplasmic organelles with no evidence of senescent or degenerative changes (Fig. 4). In this same area, several intraepithelial pseudocysts were also apparent (Fig. 5). The cells lining these pseudocysts had retained the corrugated characteristics of their surface microprojections, and the material within the cystic cavities was finely reticulated and similar to that adherent to the plasma membrane surface (Fig. 5 inset). Multiple small spherules (about 0.1 μ m diameter) were also among the contents of the pseudocysts and resembled the secretory vesicles frequently evident in corneal and conjunctival surface cells. A similar electron microscopic configuration has been observed in other intraepithelial pseudocysts of the conjunctiva.³

Discussion

The incidence of epithelialisation of the anterior chamber after penetrating ocular injury or surgery

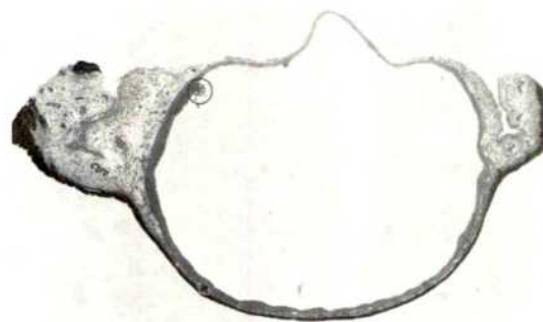


Fig. 2 Light micrograph of entire surgical specimen discloses single cyst with epithelial lining and serous contents implanted in anterior iris stroma. Nasally a nodule of the lining epithelium shows desquamation of its surface cells (circled) (paraphenylenediamine; $\times 16$).

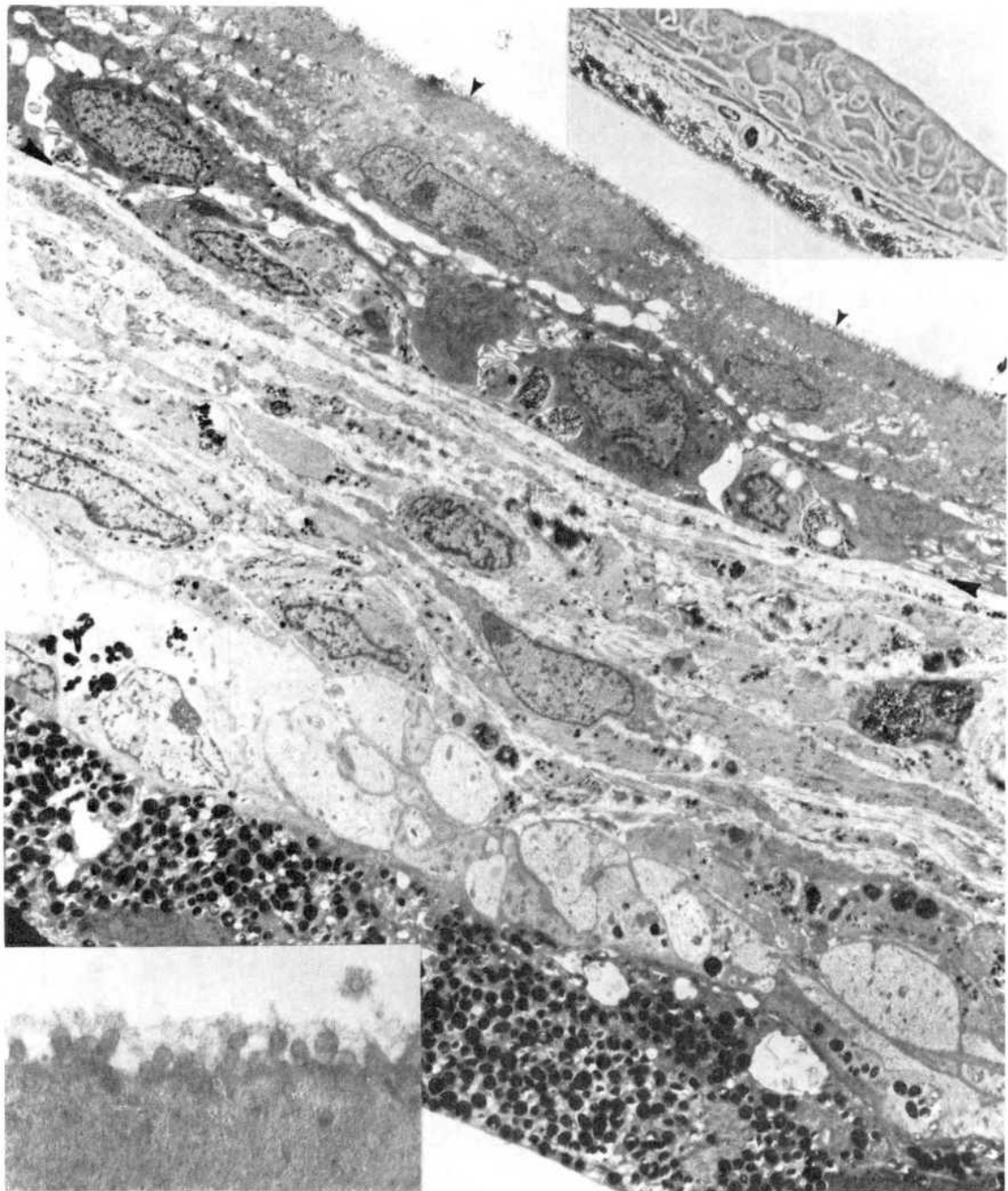


Fig. 3 Inset (top right) is light micrograph of posterior wall of lesion, showing multiple layers of stratified, nonkeratinising epithelium overlying attenuated iris stroma, dilator muscle, and pigment epithelium (paraphenylenediamine, phase contrast; $\times 400$). Main figure electron micrograph of same area illustrates numerous surface microprojections (small arrowheads) of epithelial cells exposed to lumen of cyst, small melanosomes within intermediate and basal cells, and melanocytes along basement membrane plane (large arrowheads). Normal appearing iris stroma, dilator muscle, and pigment epithelial cell layers are included ($\times 3000$). Inset (bottom left) is higher magnification of epithelial cell surface to resolve microvilli with adherent filamentous material ($\times 25\,000$).

has been recorded as 0.06% ⁴ in one large series of 45 500 patients. In a clinical series of 8 062 cataract extractions Theobald and Haas⁵ reported an incidence of 0.11% of anterior chamber epithelial invasion. Reports of epithelialisation of the anterior

chamber following keratoplasty are rare. Leibowitz *et al.*⁶ demonstrated the presence of retrocorneal epithelial cells in a patient with delayed wound healing and iris adhesion to the wound who subsequently developed an epithelial cyst. Bennett and

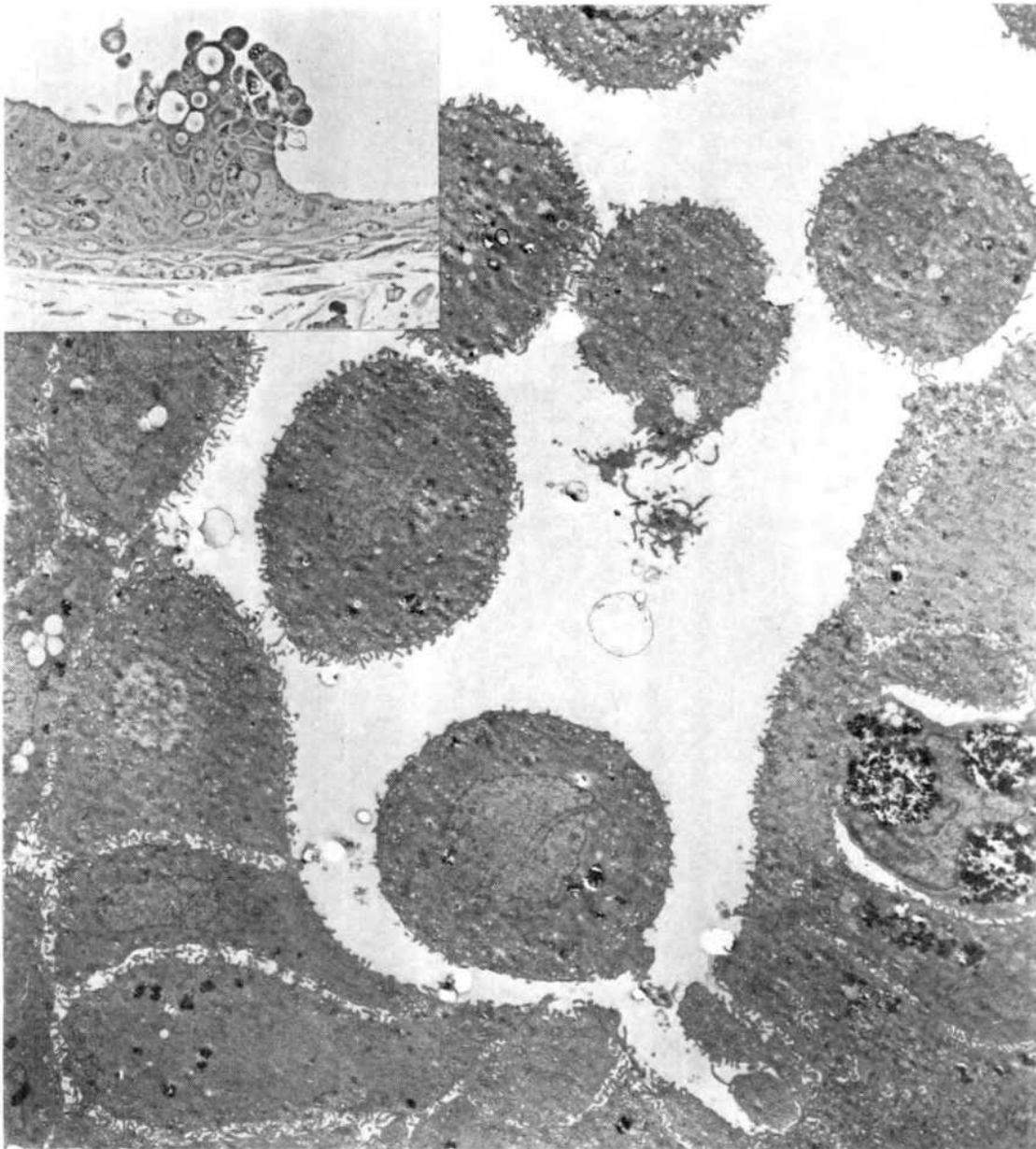


Fig. 2 Inset light micrograph illustrates nodule of acanthotic epithelium exhibiting surface desquamation and intraepithelial cyst formation (paraphenylenediamine, phase contrast; $\times 400$). Main figure electron micrograph shows these desquamating surface cells to appear normal and viable with respect to intactness of plasma membranes and cytoplasmic contents ($\times 4000$).

D'Amico⁷ also reported an epithelial inclusion cyst that was verified histopathologically following keratoplasty in an eye with episodic iritis. Experimentally, epithelialisation has been produced as ingrowth, pearl tumour, and implantation membranes but not as an isolated implantation cyst.^{8,9}

It is generally agreed from both clinical and experimental observations that the onset and exacerbation of epithelial growth is unpredictable. While growth is likely to be slow, it is imperative to

observe epithelial lesions in the anterior chamber regularly for signs of progression. If such progression is reported, then surgical intervention is indicated. The goal of therapy is complete excision of the lesion if possible without release of free, potentially viable epithelial cells into the anterior chamber. Transformation of epithelial cysts in human eyes to epithelial ingrowth and from pearl tumour to serous cyst after instrumentation have been reported.^{10,11} Subjective postoperative complaints such as glare or distortion are secondary considera-

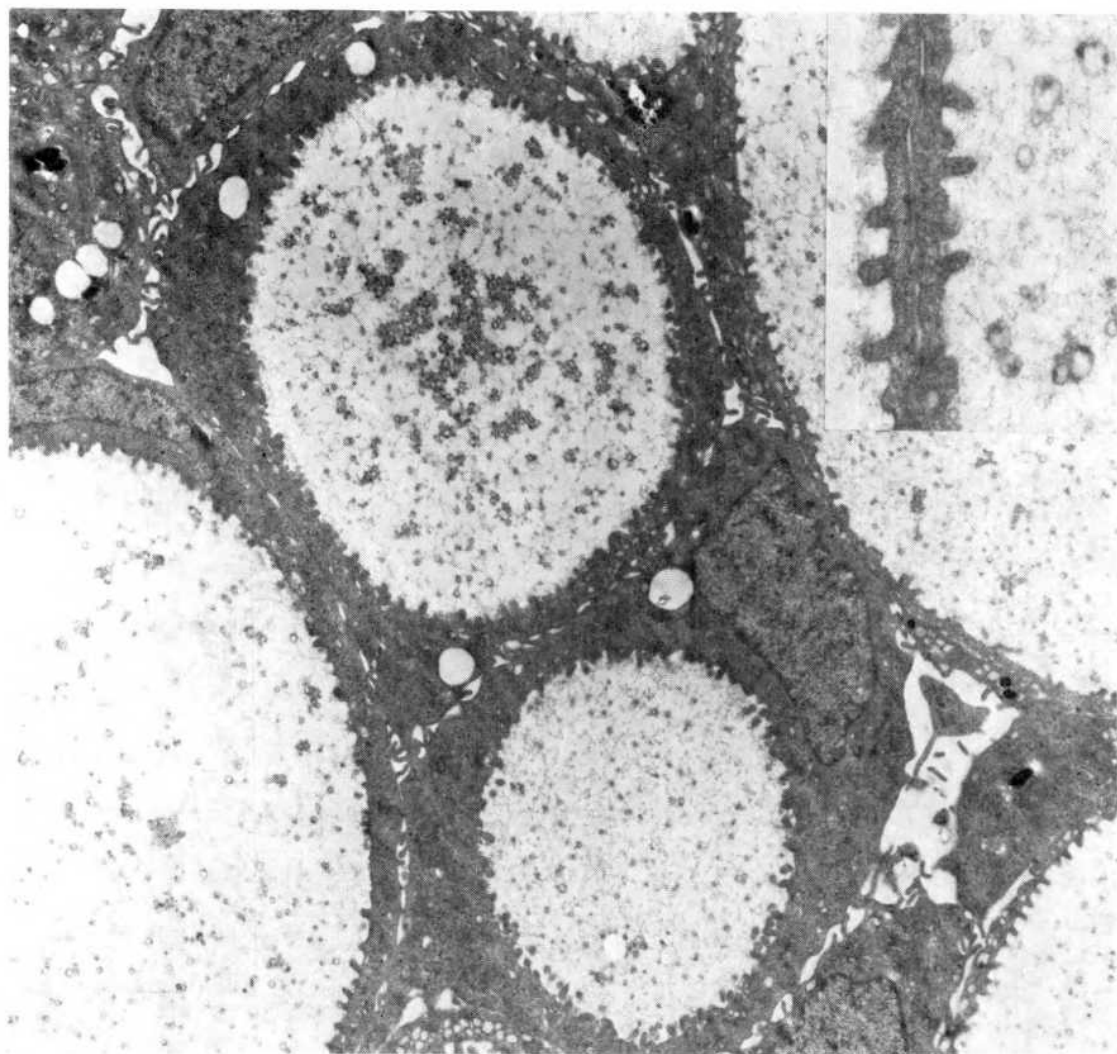


Fig. 5 Electron micrograph of cystic area reveals multiple intraepithelial pseudocysts, lined by nonkeratinised epithelium and containing fine granular and vesicular material ($\times 7000$). Inset focuses on 2 attenuated epithelial cell processes demarcating adjacent pseudocysts. These cells exhibit microvillous surface projections of their plasma membranes that are coated with fine filaments appearing similar to the contents of the cysts. Vesicular material is presumably glycoprotein or mucopolysaccharide secreted by these epithelial cells ($\times 33\,000$).

tions in view of the devastation that intraocular epithelial proliferation might cause.

In the case reported here a serous cyst of the iris followed an apparently uncomplicated penetrating keratoplasty without the predisposing features of wound healing problems, iris adhesion, hypotony, or epithelial communication with the wound. We believe the case represents an implantation of conjunctival epithelium rather than ingrowth. We concur with Ferry¹² and Bennett and D'Amico⁷ concerning the possibility of inadvertent implantation of free epithelial cells by forceps or surgical instruments during keratoplasty.

Many therapeutic approaches have been advocated for managing epithelial cysts in the anterior chamber. Aspiration (with or without cauterisation), while sometimes successful, is usually only a temporising measure, since recurrence is common and can lead to epithelial downgrowth.¹⁰ Marsupialisation, photocoagulation, electrolysis, and cryotherapy suffer similar disadvantages. Radical anterior segment reconstruction, while perhaps necessary for complete excision of an extensive lesion, may not be required if the lesion can be removed in toto while still small.¹³

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The iris naevus (Cogan-Reese) syndrome: light and electron microscopic observations

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SUMMARY The light and electron microscopic findings in an eye enucleated from a 38-year-old woman with iris naevus (Cogan-Reese) syndrome are presented. The clinical manifestations of this disease, namely, iridic stromal matting, iridic nodule formation, and unilateral angle-closure glaucoma, appear to be secondary to an endothelial membrane on the anterior surface of the iris. The iris naevus syndrome is now thought to represent one end of the clinical spectrum of an irido-corneal endothelial syndrome which also includes those clinical entities classified previously as Chandler's syndrome and essential iris atrophy.

The iris naevus (Cogan-Reese) syndrome is an entity characterised by unilateral glaucoma typically found in young to middle-aged women who develop anterior synechiae in a previously open angle.^{1,2} Iris abnormalities, including stromal matting with effacement of normal surface architecture, ectropion uveae, multiple pigmented iris nodules, and naevi of the anterior iridic surface are characteristic findings.

It has recently been suggested that the iris naevus syndrome, Chandler's syndrome, and essential iris atrophy represent the clinical spectrum of a single disease whose underlying pathogenetic mechanism is an abnormal proliferation of corneal endothelial cells leading to secondary iris abnormalities. The secondary iris manifestations seen clinically in this iridocorneal endothelial (ICE) syndrome are thought to result from variations in the pattern, rate, and extent of endothelial proliferation.³⁻⁵ The light and electron microscopic findings reported here suggest that the iris alterations of the iris naevus syndrome are secondary to an endothelial membrane on its anterior surface.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Patient and methods

CASE REPORT

A 35-year-old woman was first seen in April 1974 with a history of pain, pupillary irregularity, and heterochromia iridis in her left eye of several months' duration. The visual acuities were 20/20 OD and 20/50 OS. Ophthalmological examination revealed mild corneal oedema, ectropion uveae, and multiple small pigmented iris nodules in her left eye. The right eye appeared normal. The intraocular pressure was 16 mmHg OD and 70 OS by applanation tonometry. The positive findings were confined to the left eye. Total peripheral anterior synechiae occluded the anterior chamber angle. The optic disc was deeply excavated. The visual field showed marked constriction.

No stigmata or family history of neurofibromatosis were found. The results of serum calcium and phosphorus and serum protein electrophoresis were normal. Chest x-ray showed no abnormalities. After a short unsuccessful trial of pilocarpine and acetazolamide a posterior lip sclerectomy with peripheral iridectomy was performed under a scleral flap. The intraocular pressure remained controlled without medication until December 1974. At this time the filtering bleb was smaller than previously noted and the intraocular pressure was 27 mmHg. Epinephrine and subsequently pilocarpine were started. In August 1975 the vision in her left eye

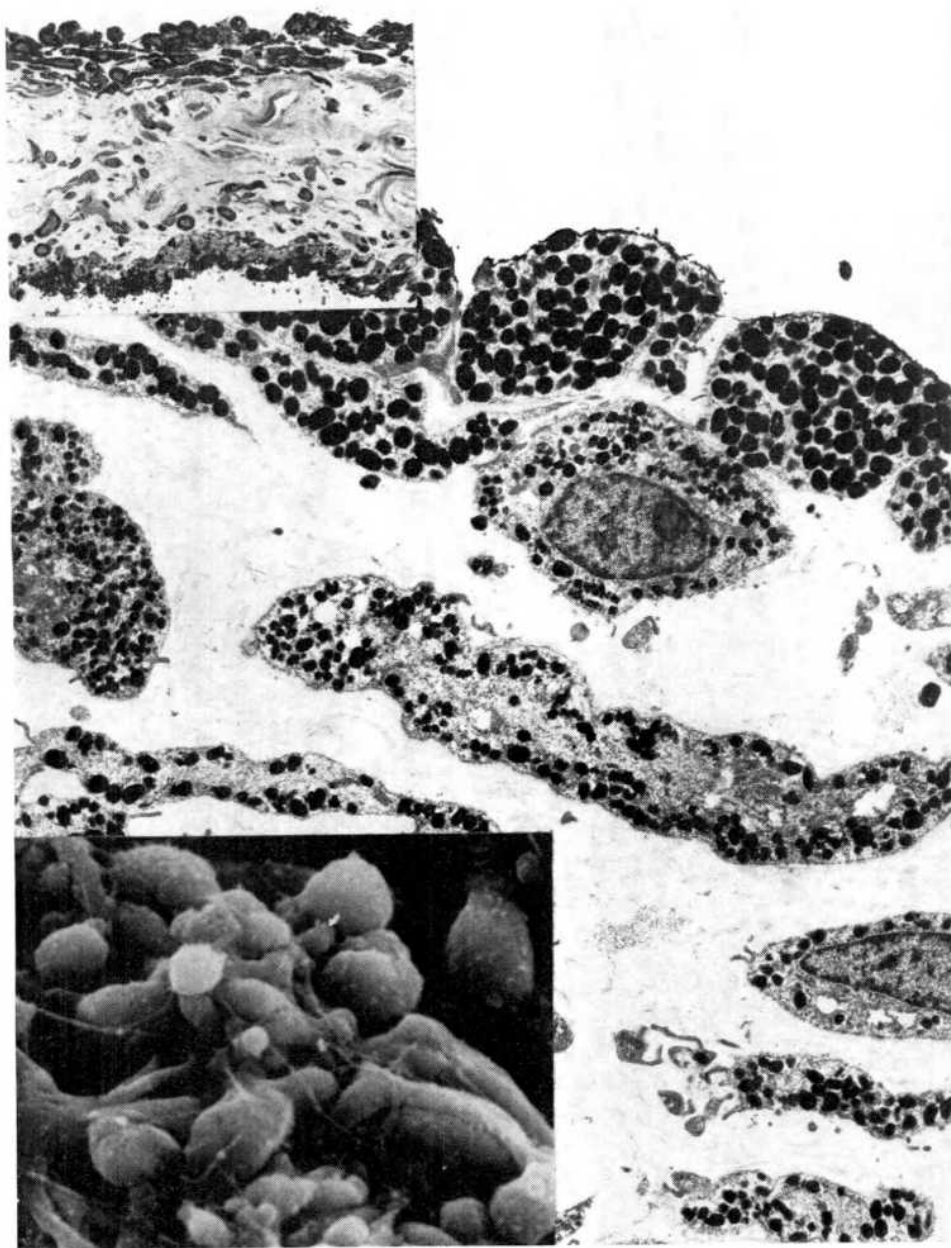


Fig. 1 Plump pigmented cells (in nonendothelialised portion of iris) containing myriad spheroidal melanin granules are present on the anterior iridic surface. The deeper stromal melanocytes show elongated cytoplasmic processes containing smaller, round to oval melanin granules. TEM, $\times 6810$. Upper inset: globose, heavily pigmented cells on the anterior iridic surface. Paraphenylenediamine, $\times 325$. Lower inset: scanning electron micrograph from the same area discloses the round to plump configuration of the superficial naevoid cells. $\times 1540$ (AFIP neg. 79-13170-1)

Fig. 2 Cohesive plaque of naevoid cells (iris nodule) rests on surface of thick endothelial basement membrane. A thin advancing sheet of melanocytes is present on the right. The basement membrane is interrupted (between arrows). Toluidine blue, $\times 630$. AFIP neg. 78-4670



was 20/20 and the intraocular pressure was 27 mmHg. The patient, who had been taking her medications sporadically, was not seen again until May 1976. Her intraocular pressure OS was 54 mmHg, and the optic disc appeared totally cupped. Visual field evaluation could not be performed reliably. In July 1976 the filtering area appeared nonfunctioning. Maximal medical therapy with echthiophate iodide 0.125% and acetazolamide sequels failed to control the tension. One month later her visual acuity had dropped to 20/400. The patient refused further filtering surgery or cyclotherapy. In February 1977 the vision had dropped to hand motions, and the intraocular pressure was 50 mmHg. The patient complained of anorexia and paraesthesias secondary to the acetazolamide.

In July 1977 the vision was light perception. Two plus corneal oedema was present. The globe was quite hard to palpation. The patient rejected further glaucoma surgery or retrobulbar alcohol block and chose to have the left eye enucleated in July 1977. The patient's right eye continued to be totally normal.

The globe was fixed in a 10% neutral buffered formalin and submitted to the Department of Ophthalmic Pathology, Armed Forces Institute of Pathology, for histological examination.

HISTOLOGICAL METHODS

Routine paraffin-embedded sections for light microscopy were stained with haematoxylin and eosin (H and E) and periodic acid-Schiff (PAS). Bleached preparations also were prepared. Additional forma-

lin-fixed wet tissue also was submitted for scanning and transmission electron microscopy (SEM and TEM). Thick sections (1–2 μ m) for light microscopy were stained with toluidine blue and paraphenylenediamine. The specimens for SEM were dried by the critical point technique, coated with gold-palladium, and examined in the AMR 1000 scanning electron microscope. After the completion of SEM examination a portion of the specimen was resubmitted for TEM.

Results

Macroscopically the irregular pupil showed marked ectropion uveae. A peripheral surgical coloboma of the iris was present at 12 o'clock. The limbal tissues had a slight bluish discoloration in the area of the filtering cicatrix. After vertical sectioning of the globe the chamber angle was seen to be closed by extensive peripheral anterior synechiae. Numerous small, dark brown to black nodules were present on the anterior surface of the light brown iris. The lens appeared cataractous. The optic disc was deeply cupped.

Microscopically the corneal endothelium was moderately atrophic, with focal areas of attenuation. Superiorly, adjacent to a surgical iris coloboma, the endothelium had extended into the filtering bleb, where it had laid down a new layer of abnormal basement membrane (ABM) material which resembled Descemet's membrane. The angle of the deep anterior chamber was occluded by peripheral anterior synechiae of varying width. Focally the

adherent iris occluded only a portion of the filtering trabecular meshwork.

Central to the pseudoangle, endothelium and new ABM were present on the inner surface of the trabecular meshwork. Endothelium also had extended on to the anterior iridic surface, where it had elaborated a thin layer of ABM. The anterior surface of the moderately atrophic iris was flattened, with effacement of contraction furrows and crypts. The anterior iris was thickened focally by an increased number of benign-appearing melanocytic cells, which resembled naevus cells. One segment of the peripheral iris was not covered by an endothelial membrane. In this area a population of rather plump,

deeply pigmented melanocytic cells was present on the anterior iridic surface covering a layer of dendritic stromal melanocytes (Fig. 1, upper inset).

Numerous iris nodules, which were composed of pigmented cells, were found only in the endothelialised portion of the iris. These nodules were encircled by and partially rested on the surface of the newly elaborated ABM material (Fig. 2). Beneath the nodules the incomplete layer of ABM was considerably attenuated and almost devoid of endothelial cells. Continuity between the nodules and the underlying iridic stroma was maintained through a central aperture in the otherwise continuous sheet of ABM. Clumps of pigmented macrophages were noted on the surface of some iris nodules. Extensive ectropion of the iridic pigment epithelium and sphincter muscle was present. The lens nucleus showed mild, increased homogeneity, probably consistent with an early nuclear cataract. The retina showed extensive atrophy of its inner layers. The optic disc was deeply excavated and the optic nerve was markedly atrophic.

Scanning electron microscopy showed a continuous sheet of irregularly polygonal endothelial cells on the anterior iridic surface (Fig. 3). Covering the majority of the anterior iris, the membrane obscured the underlying stroma, effacing its normal pattern. The endothelial cells had scattered cilia and numerous microvilli, which were most prominent near intercellular junctions. Peripherally an island of iris stroma was not covered by endothelium. Here a population of plump to globular pigmented cells rested on the surface of the normal stromal melanocytes (Fig. 1, lower inset). In contrast to the stout processes of the latter cells, the heavily pigmented surface cells had long interweaving neurite-like processes.

Bordering the island of endothelial-free stroma, the advancing edge of the endothelial membrane had a scalloped configuration (Fig. 3, centre). Tongues of proliferating endothelium appeared to be surrounding or embracing aggregates of plump stromal cells of the iridic surface. Iris nodules were

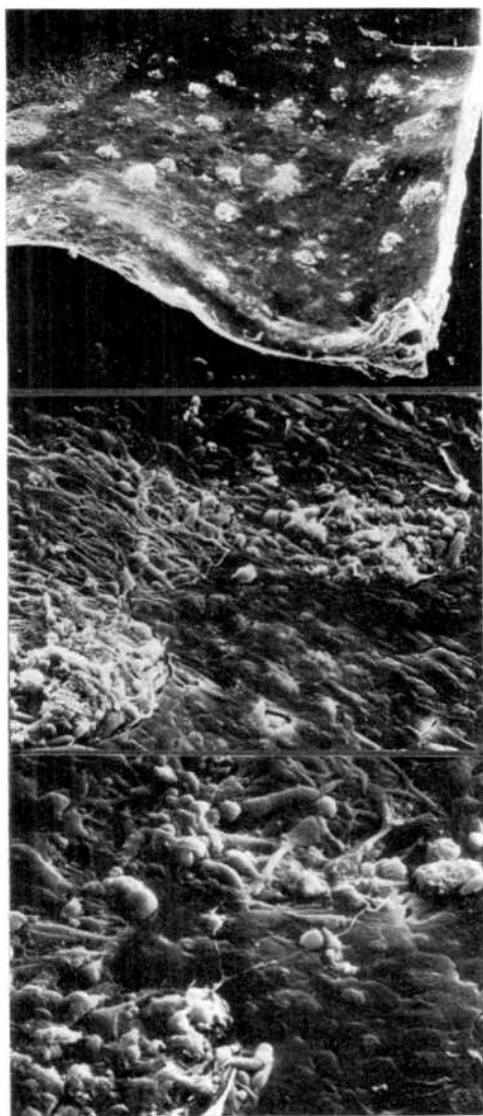
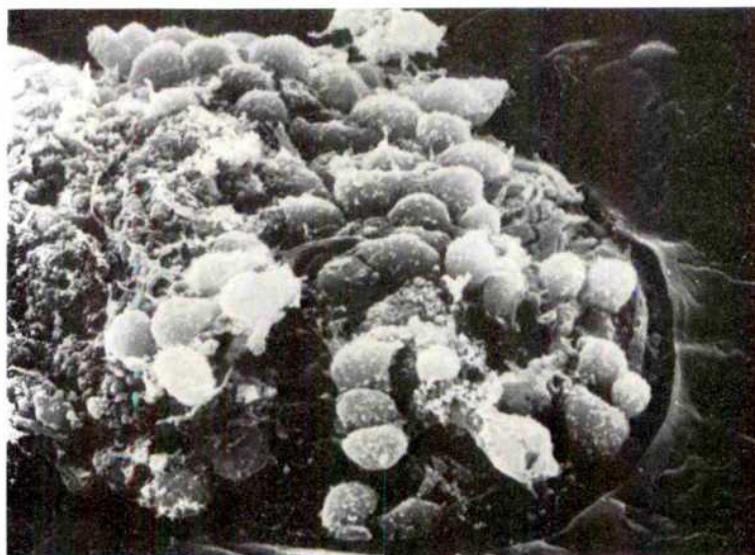


Fig. 3 Top: Scanning electron microscopy of iris surface showing effacement of architecture by a sheet of endothelial cells. Multiple well-defined nodules of melanocytic cells are present only in the endothelialised portion of the iris. Relatively normal iris architecture is seen in the upper left. SEM, $\times 28$. Centre: Edge of advancing endothelial membrane displaying smoothly scalloped border and abrupt transition to relatively normal iris stroma. SEM, $\times 257$. Bottom: Advancing tongue of endothelial membrane on the right is composed of cells with irregularly polygonal outlines. SEM, $\times 550$. AFIP neg. 79-13170-2

Fig. 4 Nodule of melanocytic cells encircled by flat endothelial membrane with sharply defined margin (on the right). Plump melanocytic cells are evident on the surface of the nodule. SEM, $\times 1216$. AFIP neg. 79-13170-3



seen only in the endothelialised portion of the iris (Fig. 3 top and Fig. 4). Generally free of endothelial cells on their surface, the round to oval nodules measured approximately 1/10th of a millimetre in greatest diameter and were composed of two cell populations similar to those seen in the nonendothelialised island of stroma. Plump melanocytic cells were especially prominent on the surface of the nodules (Fig. 4). Occasionally the cells forming the nodules appeared to extend on to the surface of the encircling endothelial membrane.

Transmission electron microscopy confirmed the endothelial nature of the cells covering the anterior iridic surface (Fig. 5). Joined by tight junctions, the cells had elaborated copious quantities of AMB, which was predominantly filamentous. Patches of banded basement membrane (100 nm periodicity) also were present (Fig. 5, inset). Two distinct populations of melanocytic cells were observed in the iridic stroma. The heavily pigmented, plump surface cells contained melanin granules that were larger than those found in the underlying stromal melanocytes (Fig. 1). The size of these granules appeared intermediate between those of the normal uveal melanocytes and the iridic pigment epithelium. The iris nodules were composed of similar melanocytic cells. A significant number of these cells had large melanin granules.

Discussion

The constellation of anterior segment findings known as the iris naevus (Cogan-Reese) syndrome usually occurs in young to middle-aged women,

who present commonly with unilateral secondary glaucoma and iris abnormalities.^{1,2} The syndrome is now thought to represent one end of the clinical spectrum of a disease that also includes Chandler's syndrome and essential iris atrophy. The basic pathogenetic event in this iridocorneal endothelial (ICE) syndrome is an abnormal proliferation of corneal endothelium that leads to trabecular obstruction, anterior synechia formation, and a spectrum of iris abnormalities, all of which are secondary to variations in the pattern, rate, and extent of endothelialisation.³⁻⁶

Characteristic iris abnormalities in the iris naevus syndrome include effacement of the normal architecture of the iridic stroma, which appears matted and smudged; pupillary distortion with extensive ectropion uveae; diffuse naevi of the anterior stroma; and multiple pigmented iris nodules.^{1,2} The light and electron microscopic findings described herein suggest strongly that these iridic manifestations are indeed secondary to endothelial proliferation, a finding which had been noted repeatedly in previous light microscopic studies.

Stromal smudging and effacement of normal surface architecture, including the collarette, result from the presence of an anterior surface naevus and a continuous sheet of endothelial cells and abnormal basement membrane material on the anterior surface of the iris. Contraction of this transparent membrane presumably leads to pupillary distortion and ectropion uveae. The fibrovascular membrane of rubeosis iridis is not usually present and therefore cannot be considered the cause of the latter 2 findings.

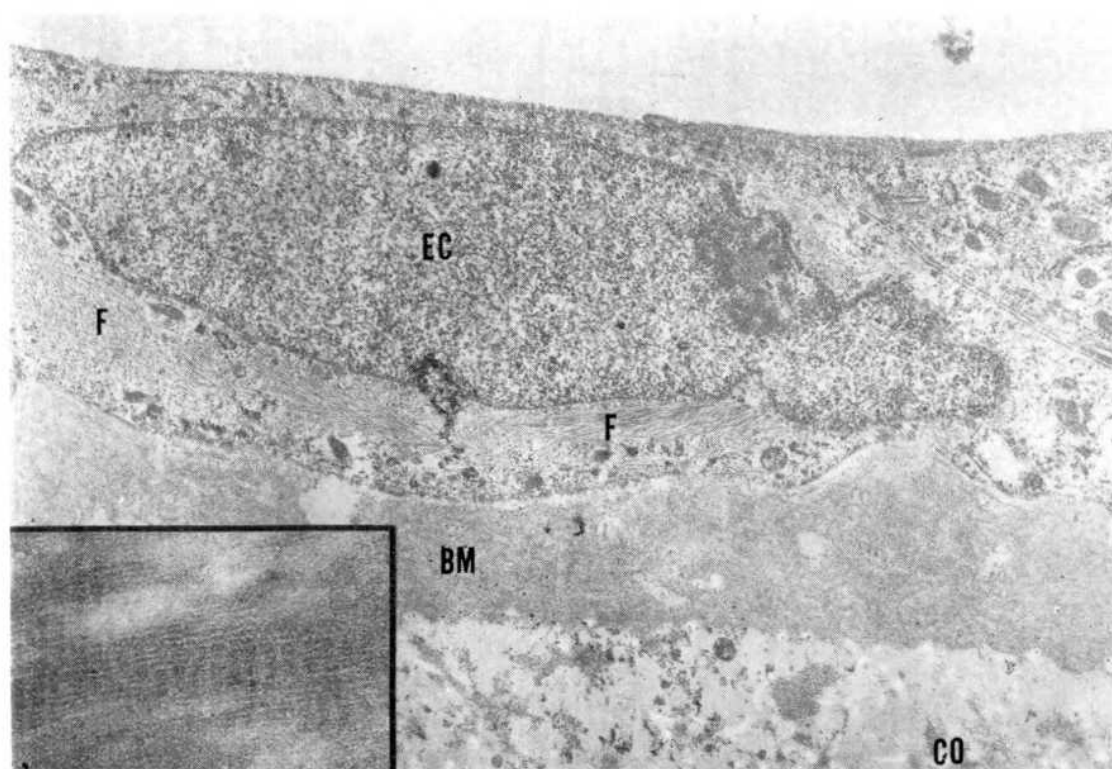


Fig. 5 Monolayer of endothelial cells (EC) resting on the iridic surface has elaborated a thick basement membrane (BM). CO: collagen; (F): cytoplasmic filaments. TEM, $\times 13\,145$. Inset shows patch of filamentous banded basement membrane with a periodicity of 100 nm. TEM, $\times 65\,300$. AFIP neg. 79-13170-4.

Endothelial proliferation probably also plays a major role in the formation of iris nodules, as originally suggested by Shields and coworkers.⁷ The confinement of nodules to the endothelialised portion of the iris, attenuation of endothelial ABM underlying the melanocytic nodules, and the presence of apertures within the basement membrane providing continuity with underlying stroma suggest that proliferating endothelium may encircle and pinch off portions of stroma. Contact inhibition between the advancing sheet of endothelium and collections of abnormal iridic melanocytes could facilitate stromal encirclement and is consistent with the scalloped border of the endothelial membrane seen by SEM. On serial clinical observation iris nodules have been noted to increase in size and pigmentation in essential iris atrophy.⁷ The extension of nodule-forming melanocytes on to the surface of adjacent ABM seen histologically suggests that these cells undergo active proliferation, though herniation of iridic stroma resulting from increasing contraction of the endothelial membrane is an alternative explanation.

Iris abnormalities usually do not occur when corneal endothelial overgrowth follows trauma or is found in association with rubeosis iridis caused by a variety of entities (for example, diabetes mellitus and central retinal vein thrombosis). This suggests that there is probably some sort of predetermined iris abnormality in the ICE syndrome. The term iris naevus syndrome was proposed by Scheie and Yanoff² to emphasise the diffuse, rarely full-thickness iridic naevi and iridic nodules composed of naevoid cells observed in those patients described originally by Cogan and Reese.¹ The plump cells with larger melanin granules demonstrated on the anterior border layer in our case probably represent a population of atypical melanocytes, that is, naevus-like cells. Jakobeic *et al.*⁸ described 2 cases with early focal iridic endothelialisation in the vicinity of discrete full-thickness iris naevi and suggested that abnormal melanocytic cells may in some manner stimulate endothelial proliferation and overgrowth onto the iris. Naevi of the iris have been described clinically and pathologically in cases previously classified as essential iris atrophy.⁹⁻¹¹

Furthermore, iridic nodules composed of melanocytic cells histologically indistinguishable from naevus cells are not infrequently seen in eyes with full-thickness iridic holes.⁵⁻⁷ It must be emphasised, however, that the naevus-like appearance seen histologically in some cases of essential iris atrophy and iris naevus syndrome could result from stromal compaction by the endothelial membrane. Further research is necessary to characterise the relationship, if any, between abnormal iridic melanocytes and the initiation of endothelial proliferation in the iridocorneal endothelial syndrome.

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Tumours of the anterior uvea. II. Intranuclear cytoplasmic inclusions in malignant melanoma of the iris

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SUMMARY Intranuclear cytoplasmic inclusions have been described previously in both human and animal tissues. So far as we are aware they are described in detail for the first time in this paper in 60 cases of malignant melanoma of the iris, usually in spindle cells. The light microscopic appearances are described, and electron microscopic studies of selected cases show clearly the genesis of these inclusions by cytoplasmic invagination of the nuclear membrane. Their significance is discussed. It is of interest that we have seen identical inclusions in malignant melanomas of the ciliary body, choroid, and conjunctiva but have not as yet reported our findings.

Although nuclear inclusions have been described on a number of occasions,¹⁻⁴ both in human and animal tissues, when they were assumed to be of viral origin, it was not until the introduction of the electron microscope that the largest group of nuclear inclusions were found to be cytoplasmic invaginations of the nuclear membrane.⁵ In an electron microscopic study of a case of tapioeca melanoma of the iris⁶ curious intranuclear pigment inclusions were described. A brief reference has also been made to cytoplasmic invaginations of the nucleus in a case of iris melanoma,⁷ but the authors did not fully document the cytoplasmic inclusions that we are describing in the present paper, the purpose of which is to report in detail the incidence and morphology of these nuclear inclusions in malignant melanomas of the iris by both light and electron microscopy and to trace their genesis by nuclear invagination.

Materials and methods

During the light microscopic study of routine sections of 199 cases of malignant melanoma of the iris, stained by haematoxylin and eosin, nuclear inclusions were observed in 60 cases. Some of the latter were examined after staining by the periodic acid Schiff (PAS) method before and after diastase treatment, by methyl green-pyronin, by the Fontana stain, and with amino acid stains. In addition 1 µm thick plastic sections of some cases were stained with

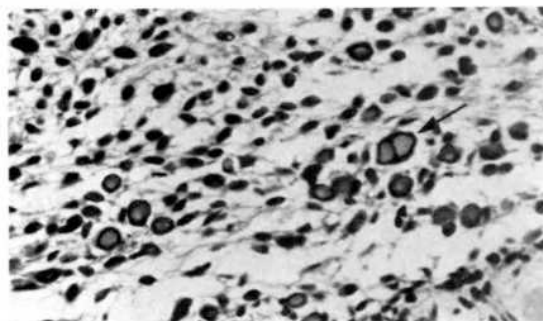


Fig. 1 Malignant melanoma of iris, showing intranuclear inclusions of varying size and shape. One nucleus (arrow) contains 2 inclusions. (Haematoxylin-eosin, $\times 245$.)

toluidine blue, and paraffin embedded sections of other melanomas were postfixed in osmium tetroxide for electron microscopic examination by the JEOL JEM-100C instrument. One malignant melanoma of the choroid was freshly fixed in glutaraldehyde and blocked in Araldite for similar studies.

Results

As stated in the previous paragraph, intranuclear inclusions were seen on light microscopy in 60 cases, 40 being females and 20 males. Fifty-seven of the tumours were spindle cell melanomas and 3 were of the mixed type. Inclusions were usually found in spindle cells. Some were small and others almost filled the nucleus; they varied in shape between spindle, spherical, and bizarre, and some nuclei contained two inclusions (Fig. 1). Some were situated

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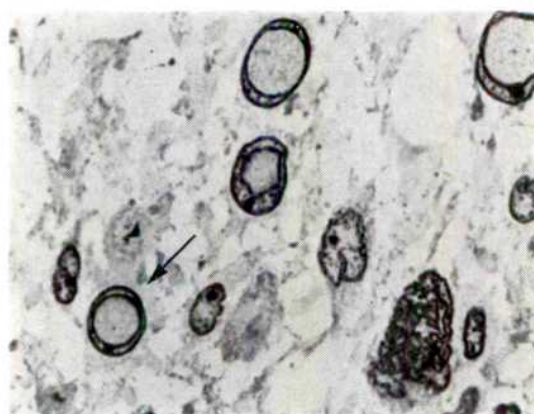


Fig. 2 Plastic section, showing centrally placed inclusion (arrow). (Toluidine blue, $\times 1440$.)

centrally in the nucleus (Fig. 2), and others were found at one pole, which was often distended. Not infrequently both the nucleus and cytoplasm become distended. The inclusions had a limiting membrane similar to the nuclear membrane and sometimes contained fine granules resembling melanin granules.

Inclusions stained with eosin with a varying degree of intensity and were PAS-positive both

before and after diastase treatment. With the methyl green-pyronin stain both the inclusions and the cytoplasm of the cells stained red. With the Fontana stain a few inclusions contained faintly staining melanin granules. The inclusions stained positively with varying intensity for tyrosine and for the sulphur-containing amino acids (Table 1).⁸

Plastic sections and electron microscopic sections showed clearly that the inclusions were of cytoplasmic origin and followed invagination of the nuclear membrane (Fig. 3). They contained cytoplasmic structures such as mitochondria, premelanosomes,

Table 1 *Histochemical staining of intranuclear inclusions*

Method (Pearse ⁹)	Result
1 PAS	Positive
2 Diastase—PAS	Positive
3 Fontana	Positive
4 Tyrosine (DC)	Positive
5 Sulphur-containing amino acids: cystine, cysteine, methionine	Positive
6 Tryptophan (DMAB)	Negative
7 Arginine (Sakaguchi)	Negative
8 Methyl green-pyronin	Pyroninophilic

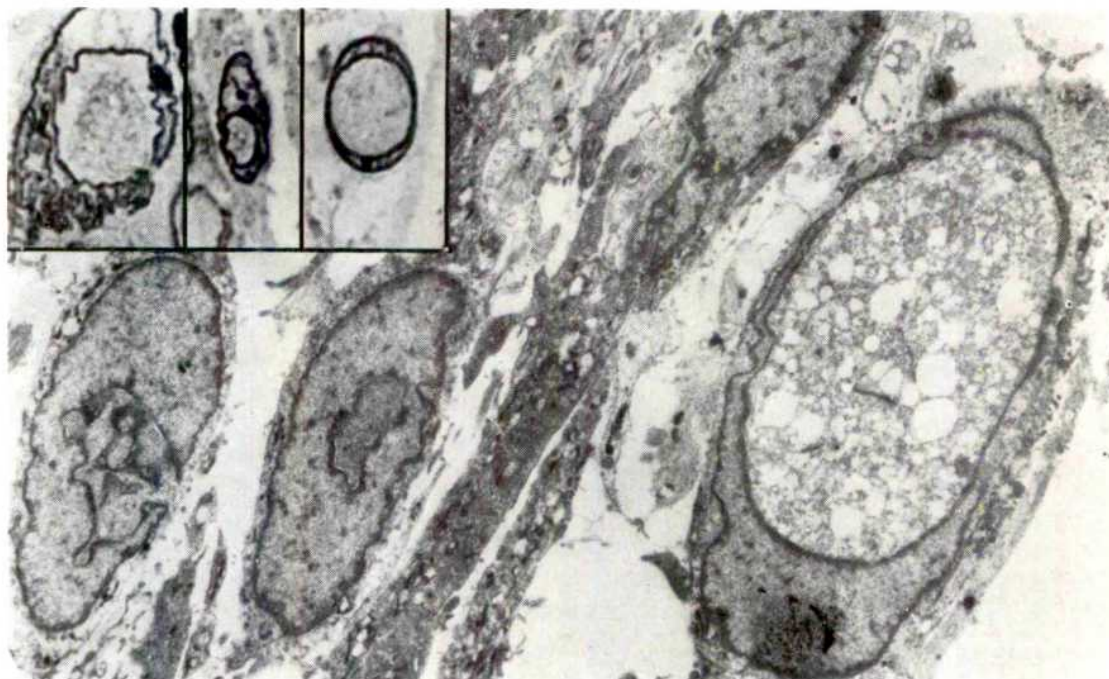


Fig. 3 Electron micrograph, showing the genesis of the inclusions by nuclear invagination ($\times 8750$). Inset are plastic sections showing similar features. (Toluidine blue, $\times 1600$.)

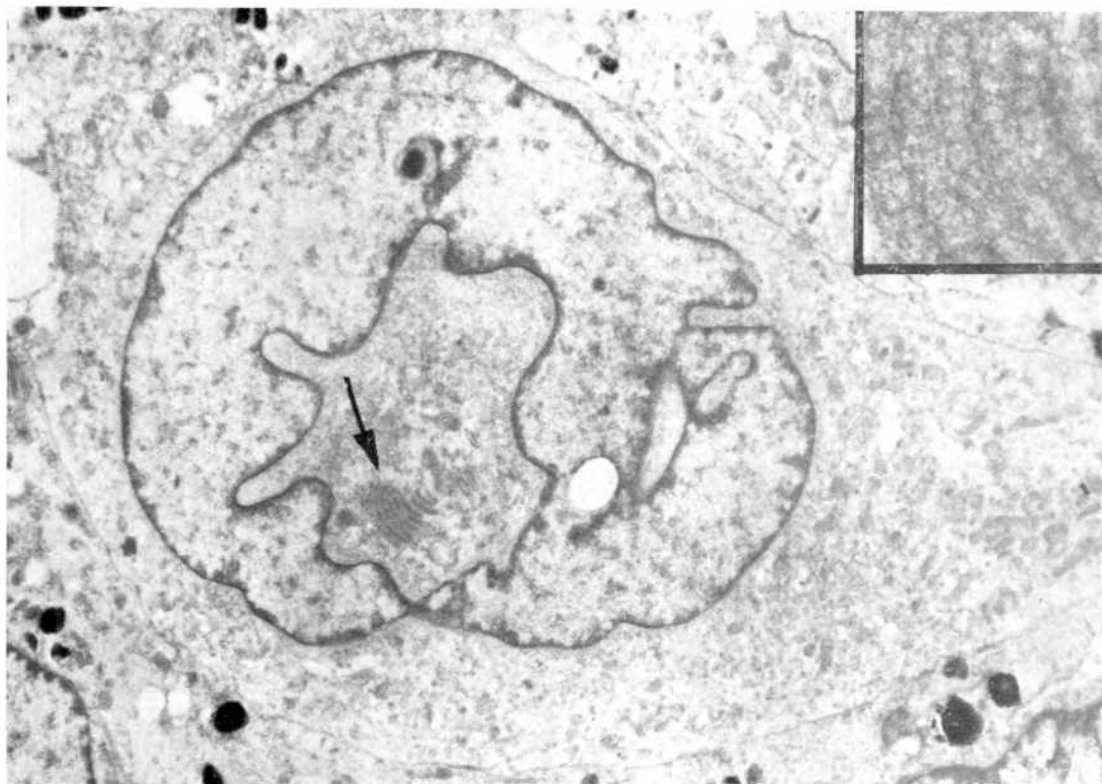


Fig. 4 Electron micrograph, showing an inclusion which contains annulate lamellae (arrow) ($\times 13\,680$) which are greatly magnified in the inset ($\times 30\,580$).

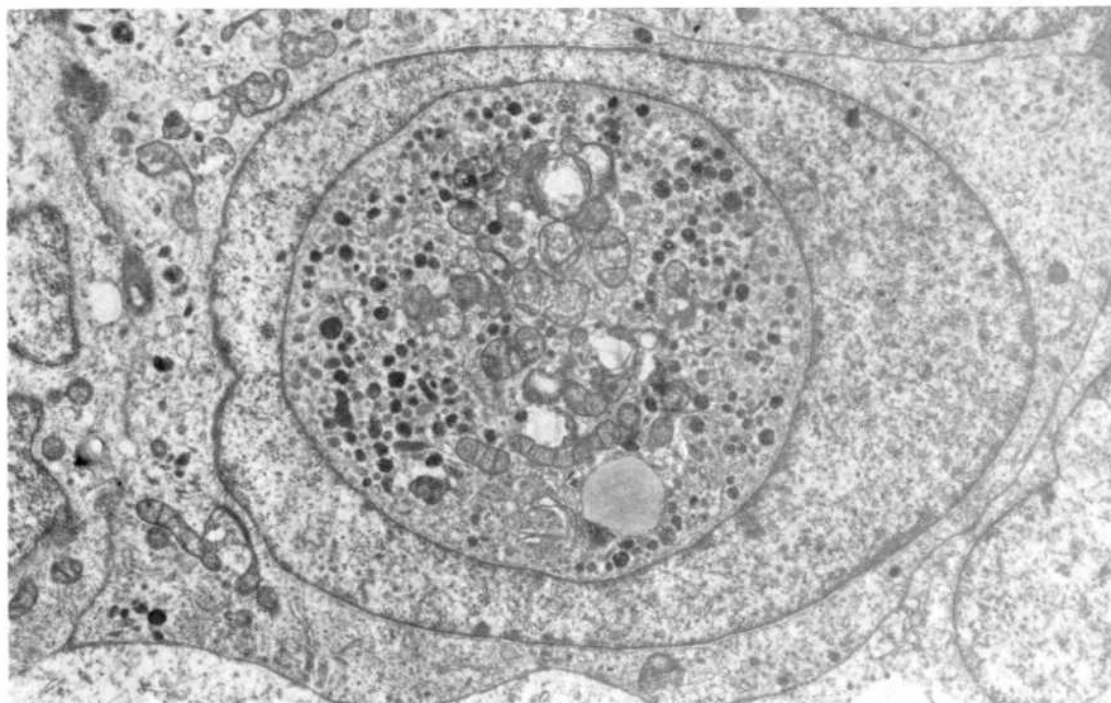


Fig. 5 Electron micrograph of a malignant melanoma of the choroid, showing a nuclear inclusion in which there are well preserved mitochondria, premelanosomes, and melanosomes ($\times 8960$).

melanosomes, microfilaments, ribosomes, rough endoplasmic reticulum, and annulate lamellae (Fig. 4), and were separated from the nuclear matrix by a double-layered membrane, the outer aspect of which consisted of condensed chromatin similar to that of the inner aspect of the nucleus. The inner aspect of the membrane was studded with ribosomes as is the outer aspect of the nuclear envelope. Electron microscopy of a malignant melanoma of the choroid showed well preserved mitochondria, premelanosomes, and melanosomes (Fig. 5).

Discussion

Although cytoplasmic intranuclear inclusions similar to those described in this paper have been reported previously,⁷⁻¹³ to our knowledge this is the first occasion that they have been described in detail in malignant melanomas of the iris. We should like to add that we have also seen very similar inclusions in malignant melanomas of the ciliary body, choroid, and conjunctiva.

The intranuclear inclusions found in malignant melanomas of the iris varied in size, shape, site, and density of staining. Although we did not carry out histochemical studies for enzymes, which are found exclusively in the cytoplasm, electron microscopy showed quite clearly that they were cytoplasmic invaginations of the nuclear membrane, so that in effect they are pseudoinclusions rather than true inclusions.

The genesis of the nuclear invagination is unknown. Some authors¹⁴ found the inclusions in large cells which contained much cytoplasm. Leduc and Wilson⁶ consider that the invagination develops as an attempt to maintain the normal ratio of nuclear surface to nuclear volume, while Sobel *et al.*¹⁵ consider that the majority of inclusions can be explained by the swollen cytoplasm extruding into the nucleus. Serber¹⁰ studied the development of cytoplasmic intranuclear inclusions in the pituitary gland of experimental animals and found that they were related to the process of aging and probably developed due to a deficiency of sex hormones.

Although we do not understand the genesis of these intranuclear cytoplasmic inclusions, we think that there may be an increase in the effective nuclear surface and the associated cytoplasm which leads to the invagination of the nuclear membrane by the cytoplasm. The significance of the annulate lamellae in some inclusions is not clear, but similar structures in the cytoplasm of normal epithelium have been identified with active protein synthesis.¹⁶ It is tempting to postulate, therefore, that these struc-

tures play a similar role in tumour cells. An active protein synthesis with consequent increase in cytoplasmic volume could lead to the cytoplasmic invagination of the nuclear membrane. Because of the finding of inclusions of different shape and size in sections of the same tumour, it is reasonable to conclude that there is a continuous process producing the inclusions.

It is interesting that 40 of our patients were females, for the prognosis from metastases of malignant melanoma of the iris is better in females.¹⁷ Is it possible, therefore, that these inclusions could be a pointer to a better prognosis in iris melanomas?

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Observer variation in ophthalmology

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SUMMARY Data collected by clinicians and nurses from patients with clinically diagnosed lens opacities revealed that there was poor repeatability of the description of the position of lens opacities, statistically significant observer variation in determining visual acuity, and good repeatability as to what visual tasks the patient can perform. It is suggested that clinicians should give more weight to the visual handicap revealed by performance of visual tasks in making a decision for cataract surgery than at present.

Ophthalmologists mainly base their decision for or against advising cataract surgery on 3 criteria: visual acuity, position and severity of lens clouding, and the effect the lenticular opacities have on the patient's life style.¹ If the criteria are to be useful, methods of using them should be valid and repeatable. That is, they should measure what they purport to measure, and they should give the same answers on repeated request. However, measures that have a high degree of repeatability are not necessarily valid.

There is little reported information on repeatability of clinical methods of assessment in ophthalmology or of questionnaire data on visual disability.² It was therefore thought desirable, while carrying out a 2-centre study into the relative severity of cataract in groups of patients,³ also to investigate the amount of variability which occurred in examination findings and questionnaire responses so that the repeatability of the currently employed methods might be assessed.

Disagreements in repeated observations on the same subjects by the same observer are termed 'within-observer error'. This may be due to inconsistency in technique or interpretation of results, and the variation tends to be random. Variation which occurs between different observers when they assess the same subjects is termed 'between-observer error', is usually due to differences in technique or interpretation, and tends to be systematic.

Two separate investigations of repeatability of clinical and interview results were carried out. The first indexed the collection of 54 separate items of information on clinical findings, personal data,

visual abilities, and past medical and ophthalmic history on 64 patients attending the Royal United Hospital, Bath, and the Bristol Eye Hospital. The second investigation was instituted to determine the repeatability of visual acuity measurements and was carried out in the outpatient department of the Bristol Eye Hospital.

Patients and methods

PATIENTS AND INTERVIEWS

Three hundred patients over 65 years old attending the outpatient department of the Royal United Hospital, Bath, and the Bristol Eye Hospital, who were noted on examination to have lens opacities which reduced the visual acuity to 6/9 or less, were interviewed and had an ophthalmic examination. All interviews were conducted by H.F.S., who also abstracted clinical data from the hospital notes and supplemented them by direct questioning of the clinician who had examined the patient. Patients who were fit enough to travel by car and who lived close to one or other of the 2 hospitals were invited to attend for re-examination; of the 300, 64 agreed to do so. Statistical examination of the data obtained about these 64 patients showed that this method of selection did not introduce bias.³

At the return visit all the 64 patients had an ophthalmic examination performed by R.A.G. with equipment similar to that used at the first examination. Interview was carried out by H.F.S. Re-examination and interview were performed without reference to the previous records in order to minimise possible bias introduced by knowledge of the original findings. The time that elapsed between first and second examination varied between three weeks and two months. Records of the first and

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second examinations were compared and the percentage of agreements for each variable calculated to give a crude agreement rate.

VISUAL ACUITY MEASUREMENTS

Two nurses employed in the outpatient department of the Bristol Eye Hospital who regularly carried out visual acuity measurements agreed to participate in this study. Patients attending the clinic for any reason were tested first by one nurse and then by the other. The two nurses examined distance vision at 6 metres with illuminated Snellen charts. A different Snellen face was used in each of the 2 testing stations. Near visual acuity was tested with Faculty of Ophthalmologists approved test types (Curry and Paxton).

So that any differences in the results of visual acuity testing such as may occur due to differences between nurses, between stations, or between first and second examinations could be assessed, a block design was used.⁴ Patients were allocated alternately to nurse 1 or nurse 2, and after each nurse had examined 6 patients the nurses changed station. This ensured that equal numbers of patients were examined by each nurse and in both stations. The distribution of patients between nurses and stations is shown in Table 1.

In comparing the first examination with the second examination differences in findings were designated positive if a smaller test type was read on the second examination and negative if a larger test type was read on the second examination. The same convention was used to compare nurse 1 and nurse 2 and station 1 and station 2.

Results

CLINICAL OBSERVATIONS

Eighteen different clinical observations were made twice on each of the 64 patients, giving in total 1152 pairs of observations. Of these pairs 207 did not agree, resulting in an overall crude agreement rate of 82%.

Table 2 shows the findings of the clinical examination.

Table 1 *Repeatability of visual acuity measurements, number of patients by station, nurse, and order of examination*

	Nurse 1		Nurse 2		Total
	Station 1	Station 2	Station 1	Station 2	
Examination 1	12	9	9	10	40
Examination 2	10	9	9	12	40
Total	22	18	18	22	80

Total number of patients = 40 = 80 eyes.

Table 2 *Examination—re-examination agreement rates for clinical findings*

Variable	Descriptive categories	Agreement rate (%)
Amblyopia	Present/absent	100
Glaucoma	Present/absent	96.8
Myopia	Present/absent	95.3
Lens	Normal/cataract/lens absent	93.8
Cataract	Mature/immature	91
Vitreous	Normal/abnormal	90
Cornea	Normal/central abnormality/peripheral abnormality	88
Retina	Normal/abnormal	79
Position of opacity	Nuclear/cortical/mixed	48

Number of patients = 64 (Bath 22, Bristol 42).

Table 3 *Agreement rates for interview data*

Variable	Agreement rate (%)
Ability to see window during the day	100
Ability to move about the house without help	100
Ability to recognise friends close up	96.8
Ability to watch television	96.8
Ability to read headlines in newspaper	96.8
Ability to do household cleaning and cookery	96.8
Ability to drive	93.7
Ability to go shopping	87.5
Ability to recognise friends across the street	84.4
Ability to cross streets unaided	82.5
Ability to recognise friends across the room	79.7
Ability to read small print in newspaper	76.5

Number of patients = 64 (Bath 22, Bristol 22).

nation. There was good agreement on the presence or absence of amblyopia, glaucoma, and myopia. The agreement on the presence of lens opacities and vitreous and corneal findings was less good. Approximately 1 in 10 was not agreed upon. Agreement rates for the diagnosis of an abnormal retina and in particular the description of position of lens opacity were much lower.

INTERVIEW DATA

At the interview each patient was asked to answer 35 questions, so that a total of 2,240 pairs of responses were recorded. 158 answers were not consistent in the 2 interviews, giving an overall crude agreement rate of 92.9%.

Table 3 shows the agreement rates for the interview data. Data on visual abilities such as reading and recognising friends had a higher agreement rate than the description of the position of lens opacity.

VISUAL ACUITY RESULTS

Disagreements between nurses over the results of distance and near visual acuity testing were spread over the whole range of visual acuities.

Fig. 1 shows the distribution of the differences of distance visual acuity measurements on individual eyes when the results of nurse 1 are compared with those of nurse 2 (between nurses), the results of station 1 with those of station 2 (between stations), and the results of examination 1 with those of examination 2 (between examinations). Approximately symmetrical distributions for these differences were found. These distributions were tested for skewedness by Wilcoxon's signed rank test,⁴ but in none of these is the distribution skewed more than might be expected by chance alone. Had the study been made with larger numbers of patients, a statistically significant systematic bias might have been revealed.

Fig. 2 also shows the distribution of the differences in near visual acuity tests, between nurses, stations, and examinations. The Wilcoxon's signed rank tests show that the distribution of the differences between nurses and between examinations are statistically significantly skewed both for the indi-

vidual eyes and for both eyes of the same patient ($P = < 0.01$ and < 0.05 respectively). This suggests that the second nurse consistently recorded patients as being able to read smaller print than the first nurse. Patients also read smaller print on the second examination. There was no significant skewing of the distribution of differences between stations.

Discussion

A search of the literature on the epidemiology of ophthalmic conditions, and in particular cataract, was made to try and find reliable methods of examination and questionnaires of visual disability. Few studies have recognised that variations in clinical assessments can occur, either between different observers or between the same observer on different occasions, despite the fact that epidemiologists have been calling attention to these problems for more than 30 years.⁵ Notable exceptions to this are the studies on glaucoma by Hollows and Graham⁶ and the carefully carried out survey of ophthalmic conditions in the Framingham eye survey.² However, studies on the prevalence of abnormal findings in the eye are still published without any reference to the repeatability of the methods used.

The results reported here suggest that prevalence estimates based on clinical examination might vary by as much as 20% between different observers, and that this variation might be much higher for specific types of retinal pathology. The variation encountered in the description of position of lens opacity was even greater.

It is unlikely that this poor repeatability was due to special features of these patients. In addition, these patients were comparable with an outpatient sample from Coventry described by Brennan and Knox.⁷ Poor repeatability of some clinical and interview data is therefore unlikely to be purely a local problem.

The repeatability of distance visual acuity tests was very low. The results of these tests showed that only a third of patients were recorded as having the same distance visual acuity on 2 occasions. Even when the results were analysed for individual eyes, fewer than half the observations on each eye gave the same results on the second test. The majority of the variation was only 1 line, but 13% of measurements on eyes differed by 2 lines or more. Near visual acuity measurements had a similar degree of variability; only a third of patients were recorded as having the same near visual acuity on both occasions. However, the range of variation was greater than for distance visual acuity measurements; 20% of all eyes were recorded as having a near visual

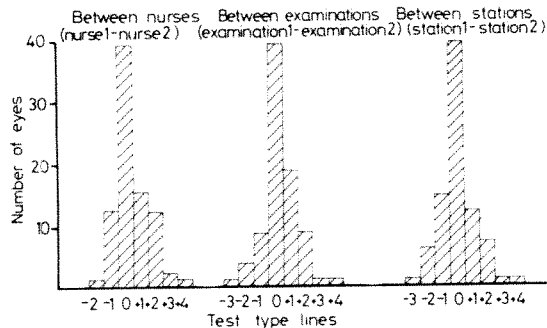


Fig. 1 Frequency distributions of test-retest differences in distance visual acuity testing

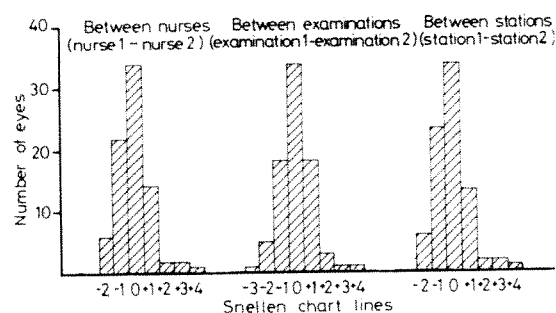


Fig. 2 Frequency distributions of test-retest differences in near visual acuity testing

acuity of 2 print sizes difference or more. Furthermore, this variation was not random, which suggests that one of the nurses was able to encourage patients to attempt smaller print sizes than the other and also that patients were more willing to try on the second test.

The clinical interview data on performance of visual tasks has a higher repeatability than the description of the position of lens opacity or visual acuity results. This may well have an implication for the clinical ophthalmologist. The visual acuity, distance and near, and severity of the lens opacity are the major criteria on which the clinician bases the decision for cataract surgery. The poor repeatability of visual acuity measurement suggests that visual handicap needs to be additionally assessed by careful questioning of the patient's ability to perform everyday visual tasks. The monitoring of patients' progress and the comparison of results with colleagues may be misleading if the poor repeatability of visual acuity measurements is not recognised.

For epidemiologists this small study may serve as yet another warning that there may be dangers in comparing groups of ophthalmic patients by the methods in current use. Studies of the prevalence of ophthalmic conditions and the comparison of groups receiving different treatments need to take

account of the degree of observer variability which may be encountered.

Our thanks are due to the consultant ophthalmologists of the Bristol Eye Hospital and the Royal United Hospital, Bath, for permission to study their patients and in particular to Mr J. C. Dean Hart for reading the paper. We are also grateful to the nursing staff in the outpatient departments of both hospitals and in particular to Nurse M. D. Thomas and Nurse L. R. Gully, who performed the tests of visual acuity.

Professor J. R. T. Colley and Mr A. O. Hughes gave valuable advice on the methodology of the study and the interpretation of the results.

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Reading type for children

G. M. MACLURE

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SUMMARY Young children experience difficulty with the present reading charts, and it may not be easy to decide whether this is due to visual problems or is associated with a deficient reading ability of the material presented to them. A reading chart has therefore been designed containing material graded according to the expected average ability for different age groups. The earlier grades use 'school script' print as well as Times Roman, which is used entirely for the older age groups. Selected words, reduced distance charts, a school script distance chart, and a standard distance chart, as well as some coloured pictures, are included.

Some children, especially those in the 4 to 10 age group, experience difficulty with the present distance and reading charts, and it may not be easy to decide whether this is due to visual problems, or whether it is associated with a deficient reading ability of the material presented to them. H. Kilmister (personal communication) wrote that it can be a problem to decide whether the patient cannot see some of the long words, and therefore cannot read them, or whether the patient does not know the long words and is unwilling to acknowledge this fact.

The writer therefore felt that it would be helpful to design a reading chart containing material graded according to the expected average ability for different age groups. Many children use some of the books in the Ladybird Key Words Reading Scheme, and are familiar with the 'school script' used in the earlier books in the series. As younger children have difficulty in reading the Times Roman print, W. Murray (personal communication) suggested using the school script for grades 1, 2, and 3 and also the level of the texts for the different age groups.

The Reading Type

The book contains: (1) The introduction, which is a summary of the rationale and usage of the reading chart. (2) Two pages of simple coloured pictures, which are not related to the following print size. (3) A page of selected words, consisting of only lower case letters, without ascenders or descenders. (4) Seven grades of reading material appropriate to each of the 7 age groups from 4-5 years to 10 and

over, and within each grade there are specimens of printing in sizes in N5, N6, N8, N10, N12, N14, N18, N24, N36, and N48. The first 3 grades (Fig. 1) are given in school script lettering of the Ladybird (sans serif) type, with simplified 'a' and 'g'. Some printing in these 3 grades is given in Times Roman for reference, as the 2 types cannot be exactly equated, and the remaining grades are in Times Roman (Fig. 2), as recommended by the Faculty of Ophthalmologists. A thumb index readily shows the level of each test. (5) A page of reduced Snellen types, school script test types, and reduced British Standard test types for comparison (Fig. 3), to be used at a distance of 35 cm. (6) A distance chart of Ladybird school script, which is very close to Times Roman in legibility coefficient, for use at 6 m, and for comparison a British Standard 6 m test type developed from Snellen.

Discussion

Each age group has been given a grade, numbered 1 to 7, so that even if a child's reading ability is not equal to that to be expected for the average age the results can still be recorded by the grade number together with the N size achieved. These can be recorded at each visit and the child's progress followed and compared. Some children may be able to achieve a higher standard of reading ability, even though their near visual acuity may be the same. For example, a child aged 5 might be able to read N6 in grade 1, and this would be recorded as such, whereas another child of the same age might only be able to read N6 in grade 3, but these results would be recorded and compared with those obtained at subsequent visits.

Law¹ suggested that reading types be standar-

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age group 5-6 years

Fig. 1

N5

Here is a dog and here is a ball.
 The dog has fun with the ball.
 I run with the dog to the shop.
 I like the sweets in the shop.
 The dog plays with the big red ball. I can get the ball.

N6

Here is a girl and here is a cat.
 The girl can play with the cat and a toy.
 They play by the big tree.
 They have fun with that toy.
 The cat can run to get the toy. The girl has fun with the cat.

N8

Here is a boy and here is a big dog.
 They have fun with the ball.
 The ball is in the water and the
 dog jumps into the water.
 The dog can get the ball from the water,
 but the boy can not get the fish.

grade
2

N10

Here is a pig and here is a tree
 I can see the pig and the big tree
 I like to play with a ball and have fun.
 Here is some water by the tree.
 The pig can go to the water.
 He can see a big fish in the water.

grade
3

N12

Here is a girl and here is a shop
 It is a sweet shop and a toy shop.
 The girl likes the toys in the shop.
 She can have fun with the toys.
 The girl can go to the shop to get some dolls.
 She can get big toys in the shop.

grade
5

grade
6

N14

Here is a man and here is a cat.
 The cat has fun with a toy.
 They are on the red rug.
 The cat can sit with the man.
 We like to see the cat have fun.
 The man has to go home to see the cat.

grade
7

Test
Types

Fig. 2

N18

The boy and his sister go on holiday. They go away to the seaside. Friends of theirs go with them to the sea. On holiday they play on the sands, and they ride on some donkeys by the sea.

N24

The brother and sister walked to a farm. They see pigs, cows and horses there. There are rabbits and a dog at the farm. The children have a friend at the farm.

grade
5

N36

On the way they pass some tall trees.

grade
6

N48

They go out in a fast motor boat.

grade
7

Test
Types

REDUCED SNELLEN TEST TYPE
For use at 35cm.

Fig. 3



REDUCED SCHOOLSRIPT
TEST TYPE
For use at 35cm.



REDUCED BRITISH STANDARD TEST TYPE
DEVELOPED FROM SNELLEN
For use at 35cm.



The letters on the above charts are approximately equal to the Snellen sizes 6/60, 6/36, 6/24, 6/18, 6/12, 6/9 and 6/6 and are for use at 35 cm. The charts on the following pages are for use at 6 m.

Test
Types

dised, and in 1952 he suggested that Times Roman type face should be used and also that the selected passages should not be of too simple a nature. While it is not desirable that they should contain many difficult individual words which the average patient can neither recognise nor understand, they should not be so simple that he is enabled to get at the word sequence. However, many young children cannot read Times Roman print, being used to books with school script print, and many words in the present near types are beyond their ability, owing to their limited vocabulary. The writer has therefore used the school script for the first 3 grades of print, but included some Times Roman to show the relationship to the recommended Faculty of Ophthalmologists standard, and written material and stories based on some of the Ladybird material but including the vocabulary to be expected for a given age group, together with a few words from the next age group. A page of single 'selected words' has been included in the book, at the request of the orthoptists, to help with cases of dyslexia and when children have problems with reading.

Youngson² stated that the methods of visual acuity testing in children, which employ symbols presented singly, while useful as a means of rough estimation or coarse screening, are no basis for a final assessment or for checking the results of treating amblyopia. As some younger children have difficulty with capital letters, a 6 m school script chart has been included, so that children can be changed from symbols to letters on a full chart which they can recognise, before going on to the capital letters, though some of the lower case letters chosen resemble capital letters. The school script has been arranged to be very close to the Times Roman in legibility coefficient, but it cannot be made identical because of the different shape and proportion of the letters, as the Ladybird school script has long ascenders and descenders. For comparison, a British Standard 6 m chart developed from the Snellen charts has been included in the book. A similar school script distance chart has been produced for rotating test types in the clinic.

Law³ recommended the inclusion of a facsimile of a Snellen distance chart reduced to 1/17th of its normal size, and Gosnell (personal communication) stated it is essential to have at least 5 test types as children learn types by heart very easily. Several reduced distance charts and reduced school script charts have therefore been included together with the reduced British Standard types. Gosnell (personal communication) also stressed the importance of using the reduced distance charts at a specified distance of 35 cm. Kilmister (personal communication) stated that the reduced distance charts for use at near point can be of great value to the orthoptists in the treatment of dense amblyopes and that they are a good comparative measurement.

Two pages of simple coloured pictures, which are not related to the following print size or to the actual test, are included to obtain and stimulate the interest of young children who might otherwise be frightened or suspicious of being tested or unwilling to co-operate initially. They are not part of the actual test.

A bar reading book has been produced for the use of orthoptists, and this uses the same principles and similar gradings and contains the other charts as well as the 2 pages of coloured pictures.

I gratefully acknowledge the help and co-operation of Mr W. Murray, headmaster, lecturer on the teaching of reading, and author of the Ladybird Key Words reading scheme, and the permission of the publishers, Ladybird Books Ltd, Loughborough, Leicestershire, to use some of the material. I also thank Mr H. J. Stockwell and Mr R. Binfield, of Clement Clarke International Ltd., for producing the Reading Type, Bar Reading Book, and the school script distance chart; Mrs P. Forbes, Miss B. L. Gosnell, and Miss H. Kilmister, orthoptists in charge, and their staff for helpful comments; Dr M. Wolffe, senior lecturer, Department of Ophthalmic Optics, University of Aston in Birmingham, for his comments; Mr K. Goult, for the photographs; and Mrs E. Silver and Mrs E. Bell for secretarial help over a long period.

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Book reviews

Computertomographie. Ed. WOLF-DIETER SAGER and GUNTHER LADURNER. Pp. 184. DM98.00. George Thieme Verlag: Stuttgart. 1979.

The incredible advances in the technique of computerised tomography that have occurred since Hounsfield first introduced the idea are amply illustrated in this small book, which is a collection of papers delivered at a symposium held in Graz in 1978. The principles and clinical applications of the technique are described, and there are sections on neuroradiology and computer tomography of the chest and abdomen. For the ophthalmologist the chapters on intracranial diagnosis will be valuable and serve to demonstrate what impact this investigation has on neurophthalmology and what advantages it has over many of the alternative methods of diagnosis.

T. J. FFYTCH

Documenta Ophthalmologica Proceedings Series. Vol. 21. First International Congress on Cataract Surgery, Florence, 1978. Eds. J. FRANCOIS, A. E. MAUMENEE, I. ESENTE. Pp. 561. US\$121.05. Junk: The Hague. 1979.

The management of cataracts has a never failing interest for ophthalmologists, and this excellently edited volume gives a very clear picture of the state of cataract management and particularly surgery in the western world in 1978. The congress was well planned in order to cover every aspect of the problems involved—social, medical, surgical, and optical—and the papers are divided into 7 sessions ranging between 6 and 15 papers each.

The first session deals with the social aspects of cataract and the broad principles of modern management. Of particular interest in this session was an article on the biochemistry of cataract by A. J. Bron and another broad survey of anaesthesia in cataract surgery by Ariano and Salvoni. The second session deals with cataract in the adult and covers all the technical advances which have occurred around the world, including well tried techniques with which most of us are familiar as well as phacoemulsification and ultrasonic fragmentation. In this session there are 2 particularly interesting papers, that of J. Barraquer on intracapsular lens extraction, and the other by A. E. Maumenee summing up the role of phacoemulsification. The next three sessions deal with congenital cataracts and cataracts of the young, incisions and sutures, wound healing, and surgical complications. Most of these papers are short and to the point, but again the paper by Barraquer was particularly well presented and very neatly illustrated. The last 2 sessions are concerned with the optics of aphakia and with intraocular implants. The organisers of the congress have clearly been at pains not to allow this particularly controversial part of the programme to dominate the proceedings, and the views expressed are varied and well balanced.

Most British ophthalmologists will find nothing specially new in this volume, but there are many excellently

written articles which are well worth reading. It is clear from the wide array of techniques described that there is still no clear indication of what is and what is not correct surgery for cataracts, and the widely differing views fail to show in which way cataract surgery is likely to progress over the next 20 years. There is evidently ample room for improvement and innovation.

A. D. MCG. STEELE

Gonioskopie und Goniofotografie. By W. MÜLLER and H. P. BRANDT. Pp. 163. DM88. Georg Thieme: Leipzig. 1979.

Gonioscopy has always been a difficult skill for the trainee ophthalmologist to learn, chiefly because the objective recording of the gonioscopic appearances is unsatisfactory. This volume sets out to describe the principles and practice of the technique and to display the numerous variations in normal and pathological gonioscopy. A method for goniophotography is described, and there are coloured photographs of the anterior chamber angle with a comprehensive text. Sadly the problems that beset the demonstration of gonioscopic abnormalities still exist, and the definition of many of the photographs is poor. But this is the only criticism of this excellent volume, which is to be recommended to postgraduate students and those working in glaucoma.

T. J. FFYTCH

Abhandlungen aus dem Gebiete der Augenheilkunde. Vol. 48. **Das okulomotorische System, physiologische und klinische Aspekte.** By Hans Drischel and Wolfgang Kirmse. Pp. 214. DM47. Georg Thieme: Leipzig. 1979.

The title of this comprehensive treatise on ocular movements is misleading, since almost all the emphasis is on the neurophysiology of the oculomotor system and there is very little discussion on the clinical aspects that are of interest to the practising ophthalmologist.

Several authors have contributed chapters on subjects related to eye movements and their central control, and much of the contemporary experimental work in man and animals is presented with extensive references. The text contains numerous formulae and difficult diagrams and will appeal more to the neurophysiologist and research worker than to the clinical ophthalmologist.

T. J. FFYTCH

The Mast Cell: Its Role in Health and Disease. Ed. J. PEPYS and A. M. EDWARDS. Pp. 873. £16.50. Pitman Medical: Tunbridge Wells, Kent. 1979.

As long ago as 1863 Friedrich von Recklinghausen noted granular cells in the mesentery of the frog, which Paul Ehrlich named mast cells in 1878. These cells are now recognised to be of major importance in immunopathology, and, although their link with basophil cells is not clear, they both have similarities in that they are recognised as sources of a wide range of potent biologically active substances. The mast cell is fixed in the tissue, and the basophil is a mobile circulating cell. It is now well known that the mast cell possesses receptors

for IgE antibody, so that allergen can combine with specific IgE antibody, which leads to the liberation of the active substances which in themselves can elicit tissue reactions in minute amounts.

This book contains a series of papers presented at a meeting held in Davos, which included basic scientists, pharmacologists, allergists, ophthalmologists, dermatologists, physicians, and ENT surgeons. The mast cell is a link between many disciplines and levels of research, and there can have been few occasions in recent years when the mechanisms of a single cell could have attracted groups of workers drawn from such diverse disciplines.

The mast cell with its specific membrane receptors is positioned where potentially noxious materials are likely to enter the body. It is located free in the bronchial lumen, in the bronchial and gastrointestinal mucous membranes, in intraepithelial sites, and generally in connective tissue around venules. In particular it can be found in the mucosa of the upper respiratory tract and in the conjunctiva. It is capable of producing a variety of vasoactive bronchoconstrictive and chemotactic mediators as well as active enzymes and structural proteoglycans, such as histamine, slow reacting substance, serotonin, platelet activation factor, and the products of arachidonic acid oxidation, which are converted to various prostaglandins. In addition such factors as eosinophil chemotactic factor and granule-associated enzymes such as chymase and kallikrein can be generated. Thus mast cell degranulation produces not only immediate type responses but also factors that attract inflammatory leucocytes, which destroy tissue by the action of lysosomal enzymes, a process that may be followed by fibrosis.

Much of the book involves a detailed analysis of the mast cell and its mechanism of action. The influence of sodium cromoglycate continues to attract enormous interest. A major section is devoted to respiratory diseases and inflammatory bowel disease. Representatives in food allergy, eye, skin, and ENT disease also presented material. In the section on eye diseases the role of mast and basophil cells in allergic eye disease is discussed by B. R. Jones and R. St. C. Dwyer. Papers are presented on the use of radioactive histamine to evaluate the effect of antiallergic drugs in the eye (M. M. Hennawi) and the use of sodium cromoglycate in the management of vernal keratoconjunctivitis (W. M. Doig; J. P. Dawson; R. J. Buckley). The use of a provocation test for the diagnosis of allergic conjunctivitis is described by I. Mikuni by determining the refractive index in tears using refractometry. The similarities between giant papillary conjunctivitis and vernal conjunctivitis are considered by I. A. Mackie and P. Wright, and the part played by mast cells, basophils, and eosinophils in type IV ocular allergy is discussed by A. H. S. Rahi and his coworkers.

The publication is a useful summary of recent work in mast cell structure and its relation to the inflammatory processes. The work shows that links may still exist between broadly divergent fields of endeavour in medicine and should serve as a useful work of reference for those who wish to learn about the recent advances in a rapidly expanding field of immunology.

D. L. EASTY

Anterior Segment Fluorescein Angiography. By MICHAEL H. KOTTOW. Pp. 270. \$41.25. Williams and Wilkins: Baltimore, Maryland. 1978.

Fluorescein angiography of the posterior segment has been in clinical use for some 17 years. Angiography of the anterior segment has been available to the clinician for 10 years, and it is therefore an appropriate time for an assessment of this technique to be made in investigating anterior segment disease. Although it can be helpful in the documentation of vascular patterns in corneal and conjunctival disease, it has particular value in the identification of abnormality of the vasculature of the iris. The vessels of the iris which cannot be closely observed with the slit-lamp have tight endothelial junctions similar to those of the retina, so that fluorescein angiography can demonstrate vascular damage in the form of leakage into the iris stroma or anterior chamber. At the same time ischaemic or neovascular conditions may be easily demonstrated.

Dr Michael Kottow has accumulated important information concerning the structure and function of anterior segment vessels and the photographic equipment and the techniques required to document their anatomy and pathology. The fundamentals of interpretation in both normal and abnormal angiograms are discussed in detail. Information is provided on diverse diseases affecting the anterior uvea, including intraocular inflammation, rubeosis iridis, diabetic microangiopathy, occlusive vascular disease, anterior segment necrosis, space occupying lesions of the iris, glaucoma, and retinal diseases which also influence the anterior segment. The author covers a wide field, which should be a valuable aid to the clinician who wishes to avail himself of these techniques, and to those interested in research where a complete review of the literature is required.

The book is written clearly and concisely and is well illustrated. It presents interesting and challenging concepts and highlights the potential advantages of the techniques and the possibilities which exist in correlating changes in the posterior segment with those which occur in the anterior segment. The potential value in the documentation of the various forms of anti-inflammatory therapy are now being realised. The first full summary of work carried out in the field shows that it has many interesting aspects, and it is recommended as a useful addition to the library of those interested in the dynamics of the microvasculature of the anterior segment.

D. L. EASTY

Correspondence

International Council of Ophthalmology

SIR, The International Council of Ophthalmology met in London on 19 April 1980 at the occasion of the centenary of the Ophthalmological Society of the United Kingdom.

Professor Jules François, president, Dr E. Maumenee, vice-president, Professor B. Streiff, treasurer, Professor

A. Deutman, secretary, Professor Barrie Jones (London), Professor E. Grom (Caracas), Professor J. Diallo (Dakar), Professor J. Hudson (London), Professor T. Krawawicz (Lublin), Professor M. Luntz (New York), Dr E. Malbran (Buenos Aires), Dr F. Newell (Chicago), Dr M. M. El Din Said (Alexandria), Professor H. Saraux (Paris), and Professor W. Straub (Marburg) attended the meeting.

Dr Maumenee gave a report on the organisation of the 24th International Congress of Ophthalmology in San Francisco (1982), which will be held in association with the American Academy of Ophthalmology. The main reports for the congress will be:

I. Advances in surgical techniques: (1) cornea (J. Barraquer, Bogota), (2) cataract (J. Charleux, Lyon), (3) vitreous (R. Machemer, Durham), (4) glaucoma and biological aspects of ocular reactions in surgery (S. Mishima, Tokyo).

II. Advances in diagnostic techniques and genetics: (1) electrophysiology (H. Henkes, Rotterdam), (2) ultrasonography (K. Ossoinig, Iowa City), (3) automation of perimetry and modern methods of subjective examination of the eye (F. Fankhauser, Bern), (4) modern analytic genetics and the eye (I. Maumenee, Baltimore), (5) multifactorial heredity in ophthalmology (J. François, Ghent).

Professor Deutman reported on the relations of the Council with the WHO. Our Council will be a 'liaison' between the ophthalmological societies, the International Agency for Prevention of Blindness, and the WHO and will communicate to the affiliated societies the most important information.

Professor Barrie Jones reported on the International Agency for Prevention of Blindness and Professor Miller on the International Study Committee on Teaching and Continuing Education in Ophthalmology.

The Council received an extensive report on the Standardisation of the electrophysiological examinations in ophthalmology from Professor H. Van der Tweel (Amsterdam), chairman of a committee composed of Professor Tazawa, Dr Hellner, Dr Van Lith, Dr Carr, and Dr Lawwill.

The Council is in favour of coloured labels for eye drops (or ointments): red for mydriatics, green for miotics, yellow for anaesthetics, blue for antibiotics, and brown for corticosteroids.

The Council edited the 'Perimetric Standards' which were published by Junk bv, PO Box 13713, NL-2501 ES The Hague, The Netherlands.

Two new societies, the Jordanian Ophthalmological Society and the Ophthalmological Society of Singapore,

joined the International Federation.

Finally, the Council accepted with gratitude the donation of a Duke-Elder medal by Lady Phyllis Duke-Elder.

The next meeting will be held in Acapulco (Mexico) in May 1981.

JULES FRANÇOIS

Concilium Ophthalmolog-
-cum Universale

Notes

Israel International Symposium on Glaucoma

This congress will be held in Tel Aviv, Israel, on 3-5 September 1980. It will review modern trends in glaucoma treatment. Further details from Miss Louise Neville at V.I.P. International Conference Services, 42 North Audley Street, London W1A 4PY.

SIDUO symposium

The SIDUO VIII Symposium will be held on 16-19 September 1980 at the University of Nijmegen, The Netherlands. The subjects for discussion will be vitreal pathology, intraocular and intraorbital tumours, biometry of the globe, extraocular structures, and new techniques. Further information from Miss M. van Tongerloo, Sint Radboudziekenhuis, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

Afro-Asian congress

The 7th Afro-Asian Congress of Ophthalmology will be held at Tunis on 25-29 October 1980. Further details from the Secretary, Dr A. Trabelsi, Institut d'Ophthalmologie, Tunis, Tunisia.

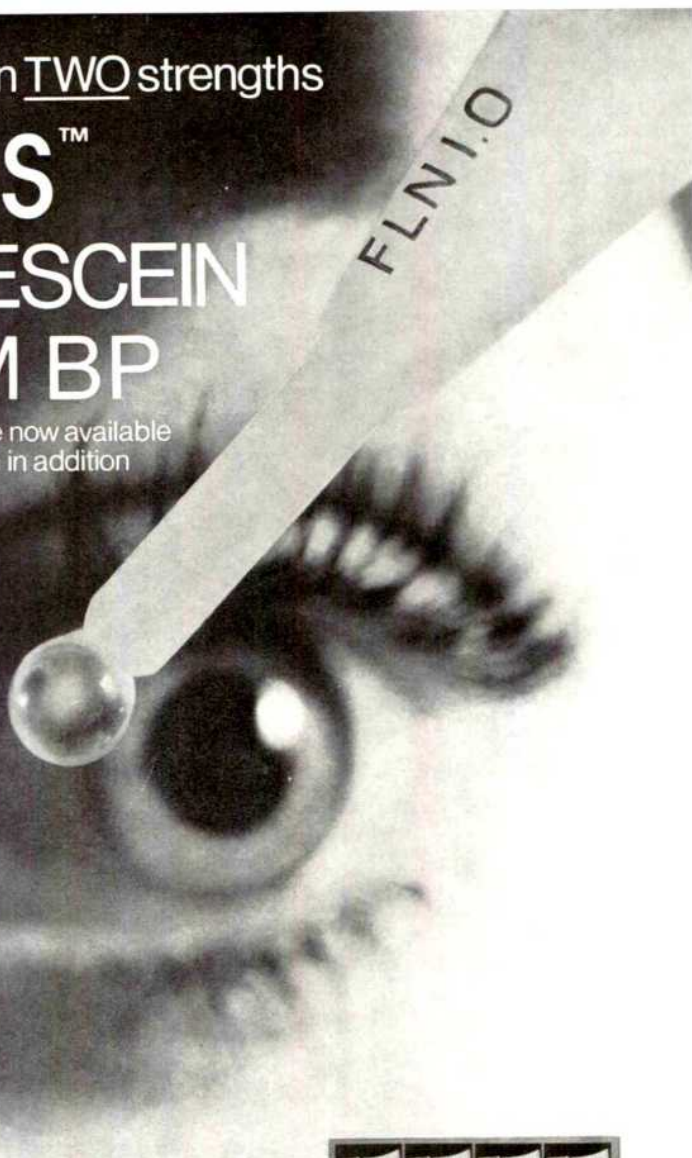
Herpes simplex infections

A symposium on human herpes simplex infections and their therapy will take place at Brest, France, on 27-28 March 1981. Subjects include biology, diagnosis, and epidemiology; antiviral drugs; nonspecific immunostimulation and interferon; and recent advances in herpetic infections in adults and children. Details from Dr Colin, Laboratoire de Virologie, Faculté de Médecine —BP 815, 29279 Brest Cedex, France.

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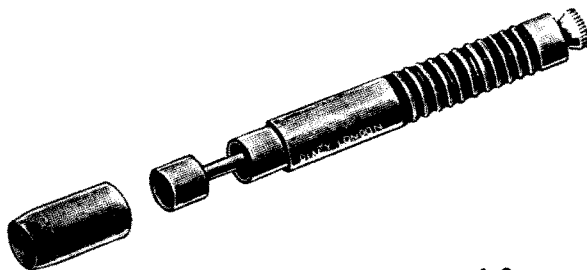
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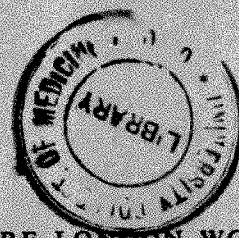
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Green AB, Brown CD. *Textbook of Medicine*. London: Silver Books, 1980.

³Grey EF. Diseases of the pancreas. In: Green AB, Brown CD, eds. *Textbook of Medicine*. London: Silver Books, 1980: 349-62.

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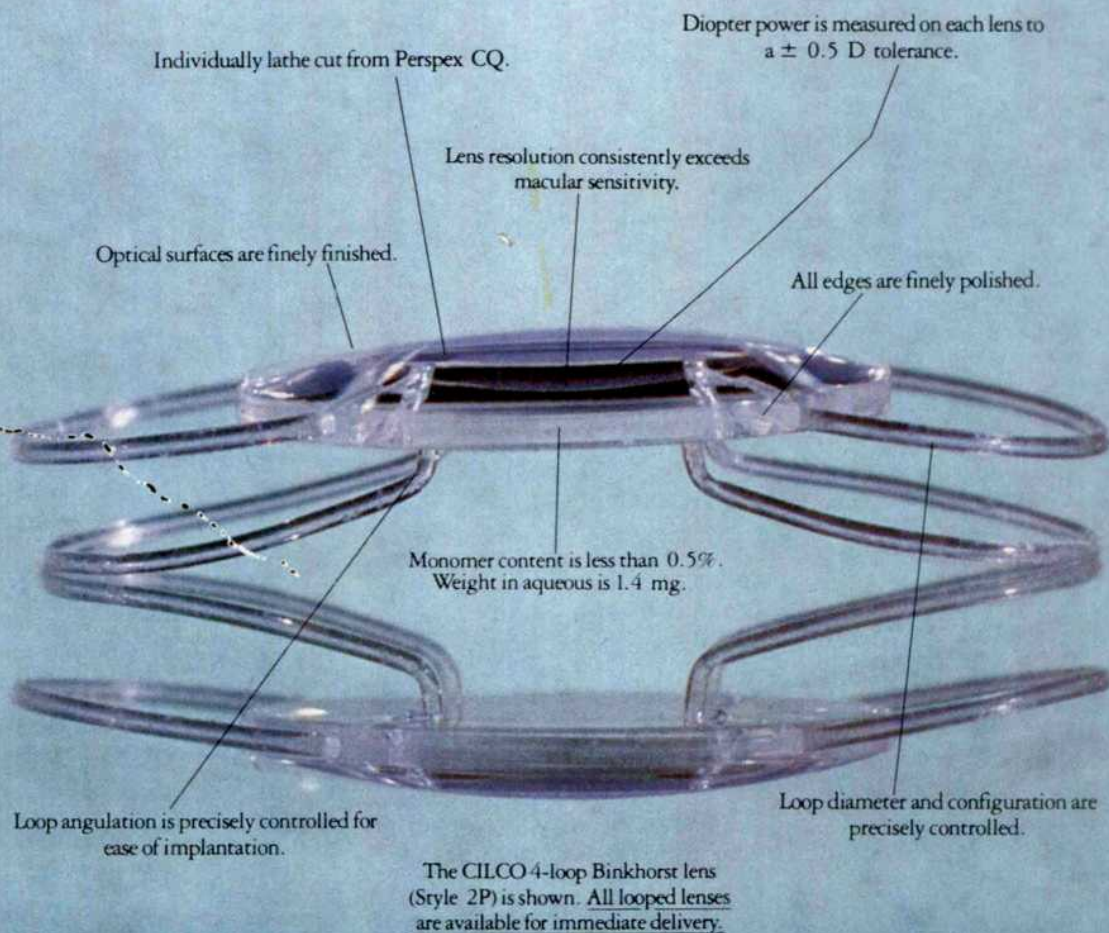
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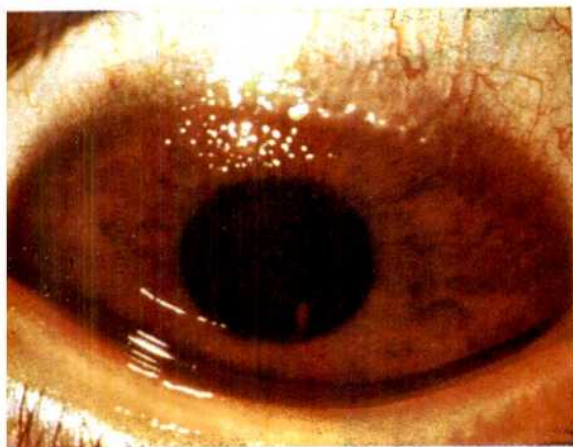
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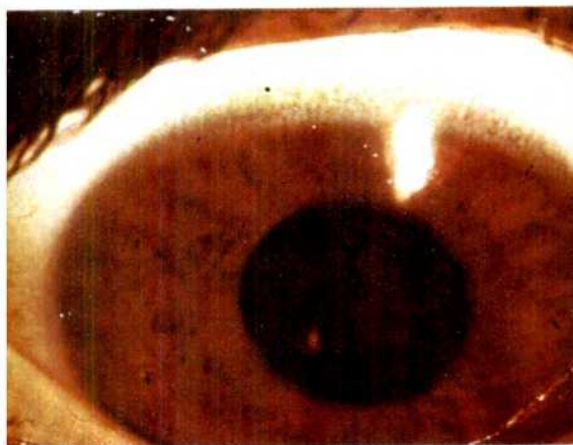
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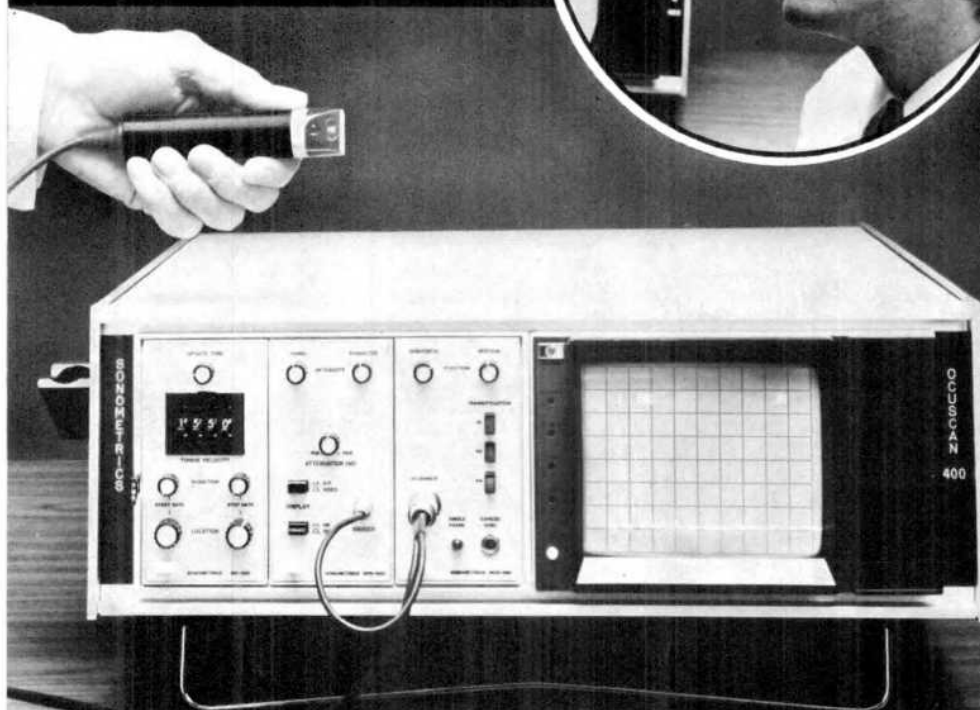
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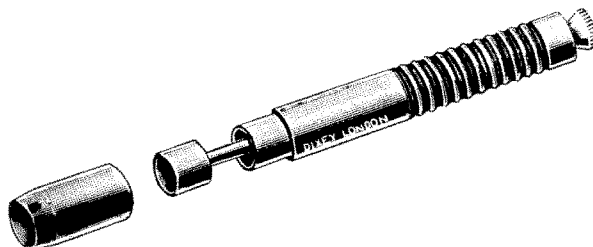
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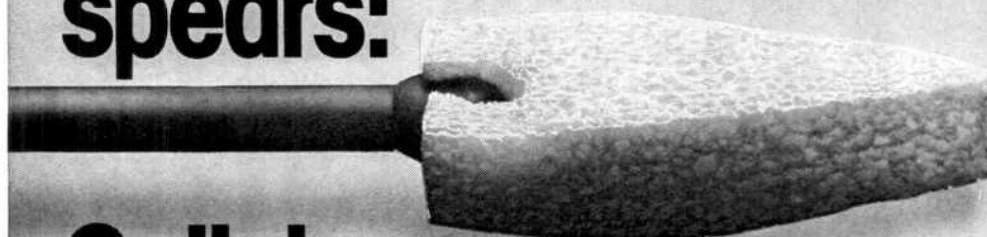
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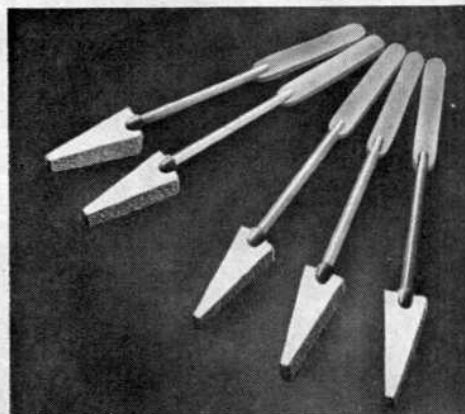


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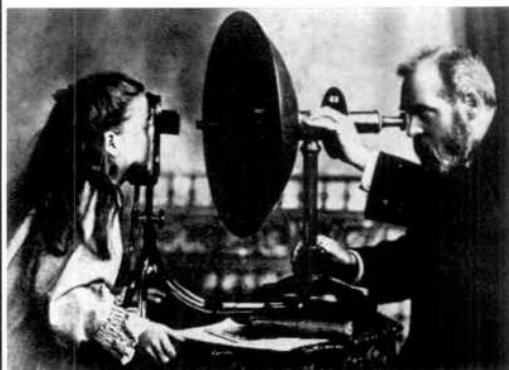
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The acute vitreous haemorrhage

JOHN S. LEAN AND ZDENEK GREGOR

From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY One hundred cases of acute vitreous haemorrhage have been analysed prospectively. It was possible to identify the cause of the haemorrhage at presentation in 79% of the cases. 40% were due to retinal tears and only 6% were associated with diabetic retinopathy.

An acute vitreous haemorrhage presents as a shower of floaters with or without blurring of vision. On examination blood is found in the vitreous cavity, either within the vitreous gel in the retrohyaloid space or both. A wide variety of conditions may lead to bleeding of this kind. In 2 recent series diabetic retinopathy was found to be the commonest cause of nontraumatic vitreous haemorrhage.^{1,2}

This paper presents an analysis of causes of vitreous haemorrhage in a prospective series of 100 consecutive cases as seen in a busy ophthalmic casualty department. We emphasise the possibility of definitive diagnosis at initial presentation in a high proportion of cases, the relatively low number of patients with diabetic retinopathy, and conversely the high proportion of cases with retinal tears.

Materials and methods

One hundred consecutive patients presenting with acute vitreous haemorrhage were entered prospectively into the study. The patients' medical and ophthalmic history, presenting symptoms, and clinical findings were recorded on a standard form. Each patient had a full ophthalmic examination including slit-lamp biomicroscopy using the Goldmann 3 mirror lens and indirect ophthalmoscopy with scleral depression. After the initial assessment in the casualty department the patients were generally admitted for further investigation and management. The case notes of all the patients were reviewed after 1 year.

Results

There were 55 male and 45 female patients. Ninety were Caucasian and there were 10 Negro.

Correspondence to Mr J. S. Lean, FRCS.

Table 1 *Causes of vitreous haemorrhage*

Cause	Percentage
Retinal tears	40
Trauma	12
Retinal vein occlusion	10
Diabetes	6
Retinal detachment	4
Retinoschisis	4
Hypertension	4
Posterior vitreous detachment	3
Malignant melanoma	3
'Vasculitis'	3
Sickle cell disease	1
Coats's disease	1
Disciform degeneration	1
Hypertension with macroaneurysm	1
Undiagnosed	4
Lost to follow-up	3
Total	100

HISTORY

66% of patients complained of floaters only. Photopsia was a relatively uncommon symptom and was seen combined with floaters in a further 15% of cases. 19% presented only with blurring of vision. 11% of patients had had a previous episode of vitreous haemorrhage. 12% gave a history of ocular trauma immediately preceding the onset of their symptoms. 5% were on treatment for hypertension and 6% were diabetic.

AETIOLOGY

The cause of the vitreous haemorrhage was diagnosed on presentation in 79% of patients. Of the remainder 14% were diagnosed on follow-up, 4% remained undiagnosed after 1 year and 3% were lost to follow-up (Table 1).

Rhegmatogenous causes. 40% of patients had a retinal tear. The majority of these (38%) were

diagnosed on presentation; the remaining 2 cases were diagnosed on follow-up and did not progress to a retinal detachment. Three patients had flat retinal tears which had been previously treated with cryotherapy. In all these cases a retinal tear was bridged by a patent retinal vessel and showed signs of vitreous traction on the operculum. In the absence of any other pathology this combination of signs was taken as evidence of the source of bleeding.

Four patients presented with acute vitreous haemorrhage as the first symptom of retinal detachment. All these patients were diagnosed at presentation.

Trauma. In 12 cases the vitreous haemorrhage was related to blunt trauma. Five patients had posterior vitreous detachment at the time of presentation. In these cases the cause of bleeding was attributed to an acute posterior vitreous detachment in association with the trauma. However, in 2 cases no posterior vitreous detachment was identified, and haemorrhage was present entirely in the vitreous gel. In the remaining 5 cases extensive haemorrhage made the assessment of the vitreous and the retina impossible.

New vessel formation. Nine patients presented with bleeding from neovascular complexes associated with a retinal vein occlusion. Six of these patients were diagnosed on presentation; 3 patients had extensive bleeding and diagnosis was only possible on follow-up. A further 6 patients had diabetes. In 3 of these there was evidence of neovascularisation, but in 1 new vessels could not be identified. In the remaining 2 patients assessment was impossible due to extensive bleeding. One patient had sickle cell retinopathy.

Retinoschisis. This was observed in 4 patients with vitreous haemorrhage. The amount of haemorrhage was minimal and tended to be in the retrohyaloid space. Abnormal paravascular vitreoretinal adhesions with punctate retinal haemorrhage were also observed in the area of retinoschisis.

Acute posterior vitreous detachment. Three patients presented with an acute posterior vitreous detachment which was recognised as the combination of posterior vitreous detachment, punctate retinal haemorrhages, and the presence of blood in the retrohyaloid space. No other ocular pathology was found in any of these 3 patients.

Hypertension. In 5 patients the vitreous haemorrhage was associated with systemic hypertension. In 1 of these patients a macroaneurysm had ruptured and in the remainder there was no apparent source of bleeding.

Miscellaneous. 'Retinal vasculitis' was associated with vitreous haemorrhage in 3 patients, though in none of these cases could definite neovascularisation

be identified. In 3 patients a vitreous haemorrhage was the initial symptom of a choroidal malignant melanoma. Two of these were diagnosed on presentation and 1 was diagnosed on follow-up. There was one case of Coats's disease, and there was one case which appeared to have bled from disciform degeneration of the macula.

Undiagnosed. Four cases have remained undiagnosed. In 1 case a large vitreous haemorrhage has failed to clear, the eye has now no perception of light, and it is assumed that the patient has a total retinal detachment. In the other 3 cases a diffuse vitreous haemorrhage was found at the time of presentation, but this has cleared spontaneously with a good visual result. No pathology has been found except that in all 3 cases a posterior vitreous detachment is now present.

Three patients have been lost to follow-up.

Discussion

In this series the commonest single diagnosis (40%) was that of a retinal tear. Only 5% of these could not be diagnosed at the time of initial presentation. The majority were fresh tears associated with the recent onset of symptoms. However, 3 patients with treated horseshoe tears bled from a patent retinal vessel crossing the tear. An earlier report³ suggested that anterior extension of the retinal tear was responsible for recurrent bleeding. In our cases the retinal vessel seemed a more likely source of haemorrhage. Such crossing vessels are prone to cause recurrent haemorrhages until they either become occluded or their course interrupted.⁴ Acute posterior vitreous detachment in the absence of a frank retinal tear was identified in a further 3 patients.

In contrast to the studies of Lincoff *et al.*² and Morse *et al.*¹ we found diabetic retinopathy to be an uncommon cause of an acute vitreous haemorrhage. We feel this partly reflects a difference in the selection of our patients. In this hospital diabetics are managed in a specific diabetic clinic and therefore tend not to present with recurrent bleeding to the casualty department. In support of this, of our 6 patients with diabetic retinopathy 5 were experiencing their first vitreous haemorrhage at the time of presentation.

Acute vitreous haemorrhage in association with retinoschisis is well recognised,⁵ although the relatively high number of cases in this series is unusual. In these patients we were able to identify abnormal paravascular vitreoretinal adhesions which appeared to be the cause of bleeding. In all cases the haemorrhage was slight and cleared rapidly.

Choroidal malignant melanomas infrequently give rise to vitreous haemorrhage. Such bleeding probably implies necrosis of the tumour mass.⁶ In 1 patient the vitreous haemorrhage was sufficiently dense that the correct diagnosis was not initially suspected.

It is interesting that systemic hypertension, although frequently thought to be associated with vitreous haemorrhage, was relatively unusual as an aetiological factor. Ten of our patients had systemic hypertension, but 5 of these were associated with a branch vein occlusion and consequent neovascularisation, 1 with a macroaneurysm which had ruptured, and in only 4 cases did the hypertension itself appear to be directly related to the vitreous haemorrhage.

This study demonstrates that the cause of an acute vitreous haemorrhage can be accurately established at presentation in almost 80% of cases.

Retinal tears form the largest single group and can be almost always identified (95%).

We thank Mr R. K. Blach for his advice and encouragement and Miss Heather Lucas for secretarial assistance.

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Management of endophthalmitis with pars plana vitrectomy

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SUMMARY Pars plana vitrectomy with intravitreal antibiotics is an effective technique in the treatment of culture-proved endophthalmitis. Best results are obtained when the therapy is instituted early in the course of infection, preferably during the first 36 hours of the onset of symptoms, and when the infective organism is of low virulence. In our 20 cases of culture-proved endophthalmitis 17 eyes (85%) were saved and had some degree of useful vision. Thirteen (65%) eyes had a visual acuity of 20/400 or better. Three eyes (15%) were lost.

Management of culture-proved endophthalmitis has been the subject of considerable therapeutic innovation. Laboratory and clinical studies have established intravitreal injection of antibiotics as an effective method of treating endophthalmitis.^{1,2} Beyond this form of treatment surgical intervention by pars plana vitrectomy has added another dimension to the treatment of endophthalmitis.^{1,3-5} This report describes our clinical experience in the management of culture-proved endophthalmitis with vitrectomy during a period of 5 years.

Materials and methods

Twenty cases of culture-proved endophthalmitis underwent vitrectomy by the Vitreous Service of the University of Illinois Eye and Ear Infirmary between 1974 and 1978. The clinical diagnosis of endophthalmitis was based on a combination of pain, periorbital oedema, conjunctival hyperaemia, chemosis, hypopyon, poor red reflex, or focal preretinal abscess. Ultrasonography and electroretinography aided in the evaluation. In cases of ocular trauma radiographs were obtained to rule out the presence of intraocular foreign bodies.

Anterior chamber and vitreous tapping were performed on all suspected cases of endophthalmitis. The samples of aqueous and vitreous were immediately inoculated on blood agar and chocolate agar plates, as well as on Sabouraud's media

for fungi and thioglycolate for anaerobes. Giemsa and Gram stains were also prepared on each specimen. After vitreous tap, a single injection of 400 µg of gentamicin and 360 µg of dexamethasone was administered into the anterior vitreous. All patients received systemic (intravenous) gentamicin for 3 days and topical antibiotics as needed.

Vitrectomy was scheduled 24 hours after intravitreal injection of antibiotics if the culture was positive. Immediate vitrectomy was performed in 2 clinical situations: (1) in bacterial endophthalmitis with extensive formation of vitreous abscess, and (2) in suspected cases of fungal endophthalmitis in which vitreous involvement was widespread and there was a delay in obtaining culture results. In both instances the deciding factor was the extent to which the vitreous clarity was involved. In such cases intravitreal antibiotics were not injected except as part of the vitrectomy surgery procedure. Surgery was performed with the patient under local anaesthesia except in apprehensive individuals. The vitrophage was used in all 20 cases. When the media were very cloudy, intraocular fiberoptic illumination was obtained with either a Fiberoptic sleeve built over the wide-angle cutter vitrophage or a separate light pipe. The technique of vitrectomy has been reported previously.¹ Vitrectomy infusion fluid routinely contained 8 µg/ml of gentamicin.

When the culture results were known, appropriate antibiotics were added to the vitrectomy infusion fluid, especially if the organism was resistant to gentamicin. When the infecting organisms were not isolated or when mixed infection was suspected, a combination of antibiotics was added

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to the vitrectomy infusion fluid.^{6,7} In cases of fungal endophthalmitis an intravitreal injection of 5 µg of amphotericin B was given after completion of vitrectomy.^{8,9} In appropriate cases systemic and topical antibiotic therapy was initiated.

Results

In our series eight culture-proved endophthalmitis cases (40%) (Table 1) occurred after previous surgical procedures. Trauma was involved in 8

additional patients (40%). Four cases (20%) developed candida endophthalmitis after intravenous drug abuse. The most common strains of organisms causing infection were: Staphylococcal (6 cases), streptococcal (4 cases), and candida organisms (5 cases) (Table 2). Aqueous cultures yielded positive results in only 15% of the specimens collected, while vitreous cultures proved positive in all cases. In 3 cases the eye was lost; 2 were infected with streptococcal organisms and one with *Serratia marcescens*.

From 14 cases of bacterial endophthalmitis only 1 (case 15) received a combination of antibiotics in the vitrectomy infusion fluid (gentamicin 8 µg/ml and clindamycin 10 µg/ml). In none of the cases did we reinject antibiotics intravitreally after vitrectomy was performed. The eyes were generally inflamed for about a week after the surgery and gradually recovered.

85% of the patients retained their eyes. 50% of eyes had a visual acuity equal to or better than 20/100, and another 15% had a visual acuity between

Table 1 Conditions predisposing to endophthalmitis

Condition	No. of patients	%
Cataract extraction	5	20
Phacoemulsification	2	10
Vitrectomy	1	5
Trauma	8	40
Following intravenous heroin injection	4	20

Table 2 Summary of patients treated with vitrectomy for endophthalmitis

Aetiology	Organisms	Interval between onset of symptoms and vitrectomy (days)	Preoperative visual acuity	Postoperative visual acuity
<i>Gram-positive organisms</i>				
1. ECLE	<i>Staphylococcus epidermidis</i>	1	HM	20/400
2. ECLE	<i>S epidermidis</i>	1	HM	20/70
3. Phacoemulsification	<i>S epidermidis</i>	1	HM	20/50
4. Trauma	<i>S epidermidis</i>	5	LP	20/50
5. Trauma	<i>S epidermidis</i>	1	HM	HM
6. Trauma	<i>S epidermidis</i>	1	LP	CF
7. Trauma	<i>Streptococcus</i> species	1	LP	NLP
8. Vitrectomy	<i>St</i> species	1	LP	Enucleated
9. Trauma	<i>St</i> species	4	LP	LP
<i>Gram-negative organisms</i>				
10. Phacoemulsification	<i>Herellea</i> species	1	LP	20/80
11. ICLE	<i>Serratia marcescens</i>	1	LP	NLP
12. ICLE	<i>Haemophilus influenzae</i>	1	LP	20/70
<i>Anaerobic organisms</i>				
13. Trauma	<i>Propionibacterium acnes</i>	52	LP	20/160
14. ICLE	<i>Clostridium</i> species	1	LP	CF
15. Trauma	<i>Peptostreptococcus</i> species	22	CF	20/25
<i>Fungal organisms</i>				
16. Heroin use	<i>Candida</i>	20	LP	20/100
17. Heroin use	<i>Candida</i>	1	LP	20/40
18. Heroin use	<i>Candida</i>	1	HM	20/50
19. Heroin use	<i>Candida</i>	1	20/200	20/25
20. Trauma	<i>Candida</i>	31	LP	20/200

ECLE indicates extracapsular lens extraction; ICLE, intracapsular lens extraction; HM, hand motions; LP, light perception; CF, counting fingers; and NLP, no light perception.

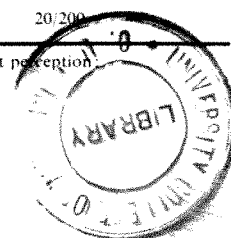


Table 3 Visual acuity after vitrectomy

Visual acuity	No. of patients	%
20/100 to 20/25	10	50
20/400 to < 20/100	3	15
Light perception to < 20/400	4	20
No light perception	3	15

20/400 to 20/100 (Table 3). 15% had light perception to counting fingers visual acuity. One eye was enucleated and 2 eyes had no light perception. These 2 patients refused enucleation.

Discussion

Intravitreal antibiotic administration and vitrectomy in the management of endophthalmitis are rapidly gaining wide acceptance.² Improved techniques of diagnosis have helped to differentiate bacterial and fungal endophthalmitis from other situations that mimic endophthalmitis, such as iridocyclitis and phacogenic uveitis.¹⁰ Conventional methods for the treatment of culture-proved endophthalmitis have not been very successful.¹¹⁻¹³ In Allen and Mangiaracine's first series¹¹ out of 22 cases of endophthalmitis only 4 retained useful vision. In their second report¹² out of 9 eyes 4 regained useful vision. In Forster's series¹⁰ out of 14 culture-proved endophthalmitis cases only 3 retained useful vision.

These poor results are explained by the relative impermeability of the blood-retinal barrier to the antibiotics, even in the presence of endophthalmitis.¹⁴⁻¹⁶ Von Sallman *et al.*¹⁷ and Leopold¹⁸ were the first to study the intravitreal use of antibiotics in the treatment of experimental endophthalmitis in rabbits. However, the use of intravitreal antibiotics was abandoned for unknown reasons.

In 1974 we reported 5 cases of culture-proved endophthalmitis that were treated by intravitreal injection.¹⁹ Since then many other reports have been published.²⁻¹⁰

We studied the role of vitrectomy in the management of experimental endophthalmitis and the maximum dose of antibiotics that could be safely added to vitrectomy infusion fluids.³ In experimental studies eyes treated with intravitreal antibiotics alone and those treated with vitrectomy and antibiotics recovered. However, the recovery was much faster and the ocular media were clearer in the eyes treated by vitrectomy and antibiotics than in those receiving intravitreal antibiotics.^{4,5}

In the present series 65% of the eyes recovered visual acuity of 20/400 or better. An analysis of our data has shown 2 factors influencing the final

visual outcome: the duration between the onset of infection and institution of therapy, and the nature of the infecting organism. Eyes infected with a marked exotoxin-producing organism had the worse prognosis. Three eyes (15%) were lost; each had an infection from an organism that was capable of marked exotoxin and proteolytic enzyme production. Results were better when therapy was initiated within 36 hours after the onset of infection, except for anaerobes and fungal infections, which progress slowly.

We recommend vitrectomy when the diagnosis of endophthalmitis is established. This is usually 24 hours after aqueous and vitreous tap and initial injection of intravitreal antibiotics have been performed. In all cases vitrectomy infusion fluid should contain a nontoxic dose of appropriate antibiotics.² In bacterial and fungal endophthalmitis, when the vitreous is severely involved, we perform vitrectomy as the primary procedure. Because of the toxicity of amphotericin B we do not recommend adding this to the infusion fluid, but it should be injected intravitreally at the end of the procedure. Recently we have evaluated the toxicity of amphotericin B methyl ester.²⁰ This compound can be added to vitrectomy infusion fluid in a dose of 10 µg/ml.

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Vitrectomy in the management of intraocular foreign bodies and their complications

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SUMMARY Twenty-six eyes with intraocular foreign bodies (IOFB) and/or their sequelae were treated by pars plana vitrectomy and associated surgery. One-step removal of the IOFB in combination with pars plana vitrectomy resulted in early visual rehabilitation and minimal complications. Of 11 eyes with IOFB treated by primary vitrectomy at the time of IOFB removal 20/50 or better visual acuity was obtained in 10 (91%). Four of these eyes had retinal injury, 3 of which were successfully repaired without subsequent complication and with retention of good visual function. In 3 eyes IOFBs were not removed owing to chronic retinal encapsulation. These eyes continue to retain good visual acuity, and ERG studies show no evidence of retinal toxicity. Of 12 eyes in which vitrectomy was performed for sequelae of IOFB only 5 (41%) showed visual improvement better than 20/50. Only in 2 of 7 eyes with tractional retinal detachment could the retina be reattached. In cases of retinal injury primary vitrectomy, cryocoagulation, and scleral buckling are suggested for prevention of late traction retinal detachment.

A magnetic intraocular foreign body (IOFB) in the posterior segment has traditionally been removed by the pars plana method,¹⁻³ the direct posterior method,⁴ or rarely the anterior approach through a corneal incision.^{5,6} In the presence of hyphaema, lens opacities, and vitreous haemorrhage and in the case of nonmagnetic IOFBs, the surgery of IOFB can present many problems.^{7,8} The use of automated vitrectomy instruments has greatly facilitated the surgery of IOFB.⁹⁻¹¹ We describe various techniques, including use of the vitrophage, by which we managed IOFB removal and associated sequelae.¹²⁻¹⁵

Materials and methods

PATIENTS

Between 1973 and 1978, 26 patients were referred to us for the removal of an IOFB or for complications caused by previous removal of IOFB. Patients ranged in age from 2½ to 60 years. All were male. The majority of injuries, caused by flying pieces of metal while hammering or chiselling, occurred when the patients were at work. The perforating

injuries ranged from self-sealing wounds to severe corneoscleral or scleral lacerations, with intraocular bleeding and vitreous and/or uveal prolapse.

For the purpose of this report we divided our patients into 3 groups. Group 1 (11 cases) had sustained recent perforating ocular injury caused by an IOFB. These patients had a 1-step operation including removal of an IOFB, vitrectomy-lensectomy, and repair of retinal injury if one was present. Group 2 (3 cases) had retained IOFB of long duration and were referred because of late complications of cataractous and vitreous opacities. Group 3 (12 cases) had an IOFB previously removed and then after varying time intervals were referred to us for management of complications, such as traumatic cataracts, vitreous opacity, and retinal detachment.

SURGICAL TECHNIQUES

Preoperative evaluation includes detailed ocular examination, appropriate x-ray studies, and ultrasound examination (mainly by B scan). In acute cases for which emergency surgery is performed cultures of the conjunctival cul-de-sac and wound margins are obtained. Local anaesthesia is used for most patients. However, children and apprehensive adults are operated under general anaesthesia.

The surgical technique depends on the nature of

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Fig. 1 *Peyman-Raichand intraocular magnetic tip with 3 mm intraocular extension (right) and 6 mm intraocular extension (left).*

the IOFB, whether it is magnetic or nonmagnetic, its size, and the presence of retinal damage. Additional factors influencing the management are damage to the lens and the extent of opacities in the vitreous. Before removal of the IOFB corneal, scleral, and other ocular injuries are treated as necessary.

A 360 limbal peritomy is made, and 4-0 bridle sutures are passed under the bellies of the 4 rectus

muscles. The scleral surface is examined to rule out occult or double perforation. A 4 mm sclerotomy, usually in the inferior temporal quadrant, is made 3 to 4 mm behind the limbus. A no. 15 Bard-Parker blade is used to cut the sclera to the uveal tract. The underlying ciliary body is cauterised. A mattress suture is passed through the lips of the sclerotomy, and a loose double-throw knot is applied. A no. 52S Beaver blade is passed through the sclerotomy into the vitreous and then removed after making a few slicing motions. In our series lensectomy was performed in all cases except case 2 in Table 3.

MAGNETIC EXTRACTIONS OF IOFB

When dealing with a magnetic IOFB an intraocular magnetic tip (Fig. 1) is introduced into the vitreous through the sclerotomy, and, if the IOFB is in the vitreous or minimally embedded on the surface of the retina, it is removed by this manoeuvre (Fig. 2). The magnetic tip is then withdrawn, and a wide-angle cutter vitrophage is introduced into the vitreous, and the mattress suture is tightened.

After a lensectomy an attempt is made to remove as much vitreous as possible. The retina is examined for retinal tears or retinal detachment which might have resulted from the IOFB or the surgical procedure. The vitrophage is removed, and the scleral mattress suture is tightened. The conjunctival peritomy is closed, and mydriatic and antibiotic drops are instilled in the conjunctival cul-de-sac.

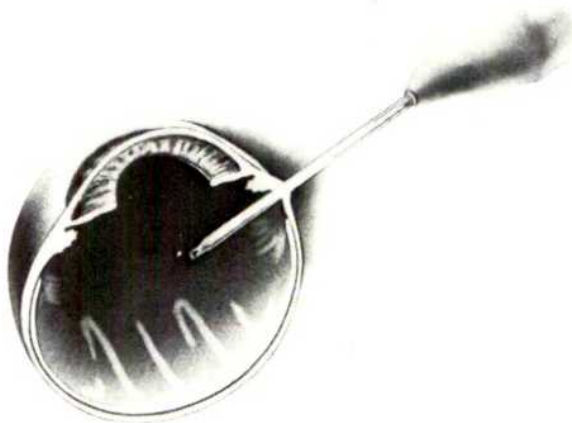
FORCEPS EXTRACTION

A standard sclerotomy is performed as described earlier and the vitrophage is inserted into the vitreous cavity. If the IOFB is floating freely in the



Fig. 2 *Magnetic intraocular foreign body extraction by intraocular magnetic tip.*

Fig. 3 Small intraocular foreign body being sucked through the cutting portal of the vitrophage.



vitreous and is less than 1 mm in size, it can be sucked through the tip of the vitrophage (Fig. 3). If the IOFB is medium sized, a pair of infusing vitreous forceps is introduced through a second

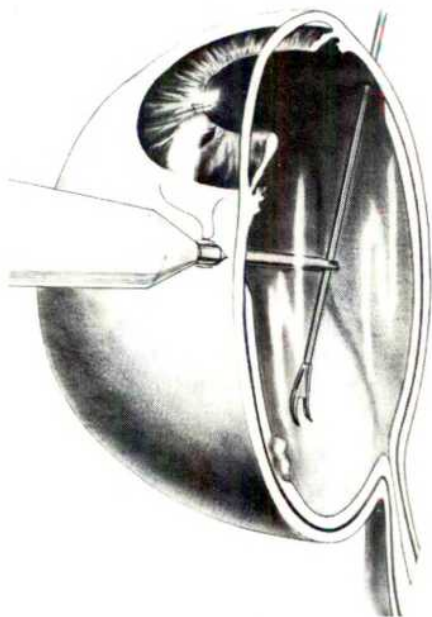


Fig. 4 Extraction by vitreous forceps of intraocular foreign body embedded in retina.

sclerotomy. After clearing the media and cutting fibrous adhesions around the IOFB, the IOFB is removed with the vitreous forceps (Fig. 4).

When an IOFB is too large to be removed through the sclerotomy, it is removed through a clear corneal incision (Fig. 5). While the assistant holds the IOFB with the vitreous forceps and the vitrophage in position the surgeon makes a clear corneal incision and removes the IOFB with the use of conventional forceps. After removal of the vitreous forceps the corneal incision is closed with 9-0 nylon suture. Vitrectomy is then completed. If the IOFB has

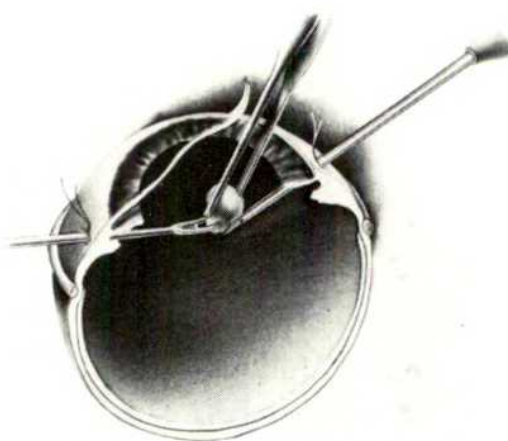


Fig. 5 Clear corneal extraction of large intraocular foreign body brought into the pupillary area by vitreous forceps.

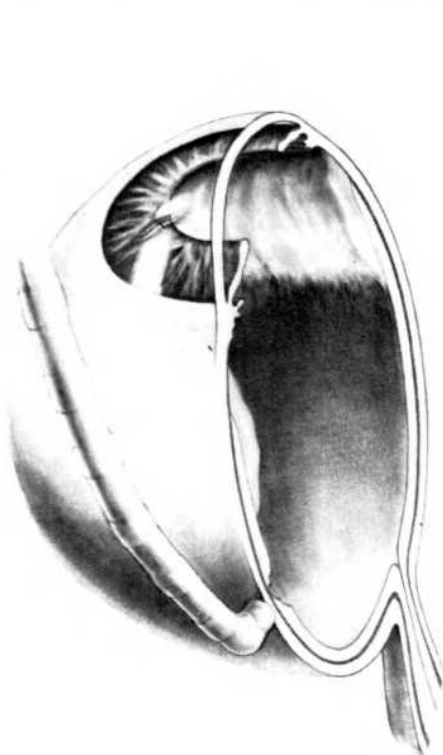


Fig. 6 Cryocoagulation around the area of a retinal injury.

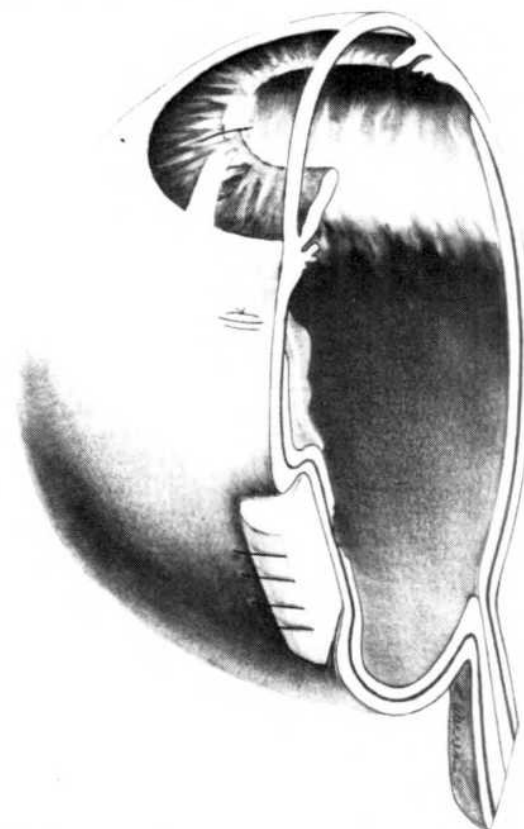


Fig. 7 Exoplastic placed over the retinal tear.

injured the retina, cryocoagulation and scleral buckling of the injured site are performed (Figs. 6 and 7).

Results

GROUP 1

Of 11 patients 5 had IOFBs that were magnetic and 6 had IOFBs that were nonmagnetic (Table 1). Of the nonmagnetic IOFBs 1 was glass and 5 were various metals. Visual improvement occurred in 10 eyes postoperatively (Table 1). Four eyes had a retinal injury caused by the IOFB. Owing to extensive injuries 1 retina could not be reattached. The retinal injury was successfully treated in the remainder without developing postoperative retinal detachment. Surgical complications included minimal bleeding from the iris in 2 cases. In 1 patient a transient rise in intraocular pressure could be controlled by medical management. Follow-up ranged from 4 months to 5 years.

GROUP 2

This group consisted of 3 cases in whom the IOFBs were not removed at the time of initial trauma. Patients were referred to us within a time interval of 1 to 4 years after the original injury. The nature of the IOFB was not known. Preoperative electroretinogram (ERG) showed no evidence of toxicity to the retina. In these patients pars plana lensectomy and vitrectomy for traumatic cataracts and vitreous opacities were done. In all these cases at the time of surgery we found a small encapsulated IOFB embedded in the retina (Fig. 8). The vitreous adhesions to the foreign bodies were cut. Because of the size of the IOFB, the long duration following the initial trauma, and the normal ERG, it was felt that aggressive removal of these IOFBs might be too traumatic to the retina. Thus they were not removed. There were no operative or postoperative complications. Visual acuity improved in all 3 cases (Table 2). Follow-up ERG examinations have remained normal over a period of 47 to 60 months.

Table 1 IOFB removal with vitrectomy-lensectomy and retinal detachment repair

Case no.	Age (yr)	Type of IOFB	Preoperative visual acuity	Postoperative visual acuity	Follow-up (months)	Retinal damage present	Operative procedure	Comment
1	21	Metal (nonmagnetic)	20/400	20/40	65	Retinal hole with localised detachment	IOFB removal through the vitrophage tip of pars plana vitrectomy-lensectomy and retinal detachment repair	Retina attached
2	43	Metal (nonmagnetic)	20/400	20/40	59	None	IOFB removal through the tip of vitrophage pars plana vitrectomy-lensectomy	—
3	21	Metal (nonmagnetic)	Hand motions	20/30	51	None	IOFB removal by vitreous forceps, pars plana vitrectomy-lensectomy	—
4	38	Metal (magnetic)	Counting fingers	Light perception	50	Total retinal detachment, retinal tear	Electromagnetic extraction, pars plana vitrectomy-lensectomy, retinal detachment repair	Irreparable retinal detachment
5	21	Metal (magnetic)	Counting fingers	20/30	37	None	Electromagnetic extraction, pars plana vitrectomy-lensectomy	—
6	30	Metal (magnetic)	5/200	20/60	31	None	Electromagnetic extraction, pars plana vitrectomy-lensectomy	—
7	35	Glass	Light perception	20/30	31	None	Electromagnetic extraction, pars plana vitrectomy-lensectomy	—
8	8	Metal (magnetic)	Counting fingers	20/25	30	None	Vitreous forceps extraction, pars plana vitrectomy-lensectomy	—
9	39	Metal (nonmagnetic)	Counting fingers	20/50	29	Retinal hole with localised retinal detachment	Vitreous forceps extraction, pars plana vitrectomy-lensectomy, retinal detachment repair	Retina attached
10	19	Metal (nonmagnetic)	Hand motions	20/30	17	None	Vitreous forceps extraction, pars plana vitrectomy-lensectomy	—
11	39	Metal (magnetic)	20/40	20/50	7	Retinal holes with localised retinal detachment	Electromagnetic extraction, pars plana vitrectomy-lensectomy, retinal detachment repair	—

GROUP 3

Twelve patients were referred to us for management of complications after the removal of an IOFB. Referrals occurred from 1 week to 4 years after initial surgery. Deterioration of visual acuity was attributed to traumatic cataract in 4 eyes, vitreous haemorrhage in 1, and tractional and traumatic retinal detachment in 7 eyes. All 4 eyes with traumatic cataracts showed visual improvement better than 20/50 postoperatively. The 1 eye with old vitreous haemorrhage showed visual improvement to 20/30 (Table 3). Of the 7 retinal detachments 2 were successfully reattached; visual acuity improved to 20/200 (Table 3). Traction on the macula accounted for reduced visual acuity in these 2 cases. In 5 cases removal of the cataractous and vitreous

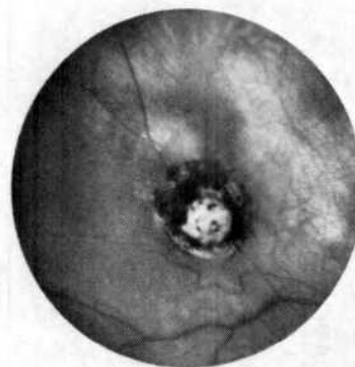


Fig. 8 Postvitrectomy. View of encapsulated IOFB.

Table 2 *Pars plana vitrectomy-lensectomy without removal of IOFB due to retinal encapsulation*

Case no.	Age (yr)	Type of IOFB	Preoperative visual acuity	Postoperative visual acuity	Follow-up (months)	Interval between injury and referral (months)	Operative procedure
1	18	Metal	20/70	20/20	60	48	Pars plana vitrectomy-lensectomy
2	20	Metal	Counting fingers	20/25	48	29	Pars plana vitrectomy-lensectomy
3	21	Metal	20/300	25/50	47	17	Pars plana vitrectomy-lensectomy

Table 3 *Vitreotomy for sequelae of IOFB removal*

Case no.	Age (yr)	Type of IOFB	Preoperative diagnosis	Interval between initial surgery and referral (months)	Preoperative visual acuity	Postoperative visual acuity	Follow-up (months)	Comment
1	9	Metal (magnetic)	Traumatic cataract	25	20/400	20/40	62	—
2	31	„	Old vitreous haemorrhage	7	20/70	20/20	60	—
3	14	„	Traumatic cataract	7	20/200	20/30	50	—
4	24	„	Tractional retinal detachment	14	Light perception	20/200	48	Dragged macula
5	35	„	Traumatic cataract	24	20/300	20/50	38	—
6	24	„	„	48	20/400	20/25	36	—
7	43	Glass	Tractional retinal detachment	36	Counting fingers	Hand motions	30	MPP
8	47	Metal (magnetic)	Large retinal tear and retinal detachment	1 week	Counting fingers	4'/200		„
9	49	„	„	„	Light perception	Light perception	28	„
10	50	„	„	2	Hand motions	20/200	24	Macular folds
11	2½	Glass	„	11	*	*	24	MPP
12	18	Copper	„	2	Counting fingers	Counting fingers	24	„

*Child. MPP = Massive preretinal proliferation.

opacities revealed that the ocular injuries had been extensive, and end stage massive preretinal proliferation (MPP) was present. Postoperative complications included transient increase in intraocular pressure in 3 eyes, which was controlled by medical means. Follow-up ranged from 2 to 5 years.

Discussion

Magnetic IOFBs are easier to manage surgically than nonmagnetic IOFBs. However, many surgical and postoperative complications can occur in both. In a large series reported by Percival^{7,8} following pars plana removal of IOFB late complications included cataract (54%), vitreous haemorrhage (37%), and retinal detachment (20%). Direct

posterior removal of IOFBs with use of a magnet was performed in 61 cases. In this group 53% developed cataracts, 39% had vitreous haemorrhage, and 20% had retinal detachments. In addition there was a 20% failure in removal of the IOFB at the first attempt.⁸

Automated vitrectomy instruments have greatly aided the management of cases with IOFBs.¹⁶ Lens opacities and vitreous haemorrhage, bands, and membranes can be removed at the time of surgery. The extent of retinal damage can be accurately assessed, and appropriate treatment can be carried out. Late postoperative complications are generally then minimised, as shown in our series.

In group 1 of our series 10 of 11 eyes treated by primary vitrectomy showed visual improvement.

Four of these eyes had retinal injury. In 3 eyes the retinal surgery was successful and had no complications over a follow-up period of 4 months to 5 years. In 1 eye, owing to the extensive nature of the injury, the retina could not be reattached.

In group 2 of our series 3 eyes had retained IOFB. After performing lensectomy-vitrectomy we did not remove the IOFBs because they were small, firmly encapsulated, and embedded in the retina. Preoperative ERGs had not shown evidence of retinal toxicity. There was a delay of up to 4 years in referral of these patients to us. Had these cases been seen shortly after the acute trauma we would probably have attempted to remove the IOFB. Interestingly, in these cases there was no preretinal membrane formation or tractional retinal detachment in spite of the retinal injury and retained of IOFB. Follow-up studies in these eyes by means of ERG examination have not shown any sign of retinal toxicity, and the eyes continue to maintain good visual acuity. These cases show that not every retinal injury leads to a retinal detachment. However, these injuries had apparently not caused extensive vitreous haemorrhage. Possibly the presence of extensive amounts of blood in the vitreous might have stimulated growth of fibrous tissue and subsequent retinal detachment.^{17,18} An initial decision to perform vitrectomy would depend on the extent of vitreous haemorrhage and the extent of retinal injuries. We do not consider vitrectomy to be urgently necessary when the media are clear enough to allow surgical removal of IOFB and allow examination of the fundus. In our opinion a retinal injury, if seen, should be cryocoagulated, and scleral buckling should be performed. Such cases may be referred later to a vitreous surgeon for vitrectomy if necessary.

Perhaps the extent and nature of the ocular injury in group 3 patients were not recognised at the time of removal of the IOFBs. The cloudy media might not have permitted adequate assessment of the intraocular pathology. Also, later changes in the vitreous could have contributed to the eventual tractional retinal detachments. Vitrectomy during the initial surgical procedure might have reduced these late complications. However, in selected cases in this category it is possible to remove vitreous traction and cut preretinal membranes by

pars plana vitrectomy to allow the retina to become reattached.

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Clinical trial with 2% sodium cromoglycate (Opticrom) in vernal keratoconjunctivitis

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SUMMARY An open assessment study was carried out during the summer of 1972 in which 2% sodium cromoglycate eyedrops were evaluated in the treatment of patients with vernal keratoconjunctivitis. A highly significant number of patients found the eyedrops effective, while a marked improvement was recorded in mild and moderate cases; in severe cases or in acute exacerbations additional steroid therapy was recommended. Sodium cromoglycate eyedrops were found to be as effective as Decadron and superior to Antistin-Privine. Furthermore SCG eyedrops could replace or reduce local steroid therapy in vernal keratoconjunctivitis and so avert the possible rise in ocular tension caused by steroids.

Vernal keratoconjunctivitis (VKC) is a severe perennial form of allergic conjunctivitis involving the cornea and conjunctiva. The condition is found predominantly in children or young adults and commonly in atopic individuals, who may also suffer from eczema, asthma, or hayfever. The disease generally affects the upper tarsal conjunctiva, which shows a papillary hypertrophy which has a 'cobblestone' appearance in severe cases. The main symptoms are severe itching and the production of a tenacious stringy mucous discharge. The limbal conjunctiva may also be affected, either as a localised oedema and hyperaemia or as fleshy isolated vegetations. It is considered to be an atopic disease¹ and has been classified as a type I allergic disease of the outer eye.²

Although VKC responds well to the instillation of corticosteroid drops, not all cases achieve complete control, and long-term use of steroids in the eye is known to produce glaucoma.³ The high incidence rate of the disease in Egypt along with incomplete amelioration with the use of antihistamines, vasoconstrictors, and steroids made the study of other possible therapeutic agents very desirable.

Such an alternative agent was sodium cromoglycate (SCG), which, in addition to its effectiveness in the treatment of asthma,^{4,5} rhinitis,^{6,7} proctitis,⁸ and ulcerative colitis,⁹ was reported^{10,11} to be effective when applied topically to the conjunctiva in

the treatment of VKC. It is thought that SCG acts by inhibiting the release of histamine and other mediators of inflammation which occurs when antigen combines with sensitising antibody on mast cells.¹²

This paper presents the results of an open assessment study carried out at Alexandria University, Egypt, in which 2% SCG eyedrops were evaluated in the treatment of VKC and its effectiveness compared with that of dexamethasone (Decadron) and a solution containing antazoline sulphate 0.5% and naphazoline nitrate 0.025% (Antistin-Privine).

Materials and methods

A total of 89 patients were selected in whom the disease had equal intensity in both eyes and the duration had varied up to 15 years. All these patients were in continual contact with the clinician through the year prior to the study and also during the whole study period. During the 12-month period only 6 patients dropped out of the trial.

The patients were divided into the following treatment groups: group I, 2% SCG eyedrops into both eyes 4 times daily; group II, 2% SCG drops into left eye, Antistin-Privine in right eye, 4 times daily; group III, 2% SCG drops in left eye, Decadron in right eye, 4 times daily.

In patients selected for this study all the other ocular therapy was deliberately discontinued 1 week before the start of the trial in June 1972. After a 1-week baseline period the clinician made subjective and objective measurements in all patients every day for the first 10 days, once a week for 6 weeks,

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and then every month for a total period of 12 months. At each of these examinations the clinician recorded his subjective opinion on the following symptoms, using a 0 to 4 rating (0=no symptoms, 1=minimal, 2=moderate, 3=moderate/severe, 4=severe): itching, grittiness, sticky and watery discharge, blinking, and congestion. A 0 to 3 rating (0=nil, 1=mild (flat topped)=mosaic, 2=moderate (small elevations with definite depressions), 3=severe (giant/or cauliflower)) was used to score the following signs: papillae on upper and lower tarsus and upper and lower fornix, follicles on upper and lower tarsus and upper and lower fornix, chemosis of bulbar conjunctiva, mucous filaments, oedema, nodules, pannus, Trantas spots, punctate epithelial keratitis (PEK), corneal ulceration, and ocular tension.

The formulation of the eyedrops used was an aqueous solution of SCG BP 2% w/v with benzalkonium chloride 0.01% w/v and 2-phenylethanol 0.4% w/v. The approach to the statistical analysis was the same for all 3 groups and made use of the paired nature of the data, namely, either before/after treatment or right/left eye. The data from each of the 3 groups were analysed separately.

Results

GROUP I

Fifty-nine patients with acute vernal disease were entered in this group. The incidence of atopy and other allergic conditions was very low (Table 1). The first patient entered in the trial was assessed in a different manner and his results have been excluded from the analysis. The total sample size for this group is therefore 58.

Comparison of the subjective and objective scores recorded before the start of the trial and after subsequent visits showed a statistically significant

Table 2 *Changes in the symptoms and signs of VKC after treatment with SCG for 1 month and 8 months (group I)*

Variable	Response	After 1 month		After 8 months	
		Right eye	Left eye	Right eye	Left eye
Efficacy	High	32	32	42	42
	Mild/moderate	23	23	13	13
	None	3	3	3	3
Side effects	Yes	4	4	7	7
	No	54	54	51	51
Patient's opinion	Satisfactory	53	54	54	54
	Unsatisfactory	3	4	4	4
Stinging or irritation	Yes	18	19	37	37
	No	40	39	21	21
Did clinical condition improve?	Yes	53		55	
	No	5		3	

cant therapeutic effect with respect to all the variables ($P < 0.01$). In addition the ocular tension was found to be significantly reduced after 8 months' treatment (see Table 4 below).

Clinical assessments made after 1 and 8 months' treatment of overall efficacy, patient's opinion, clinical response, and side effects showed that a high percentage of patients found the eyedrops satisfactory and effective. In addition the clinical condition had improved in a high percentage of patients (Table 2).

GROUP II

In this group 15 patients always received Antistin-Privine (A-P) eyedrops in the right eye and SCG eyedrops in the left on an open basis. Both treatments were administered 4 times daily. As in the patients in group I the incidence of atopy and other allergic diseases was very low (Table 1).

Comparison of the subjective and objective scores recorded before the start of the trial and after subsequent visits for the right and left eyes respectively showed a statistically significant difference in favour of SCG eyedrops. In the case of the subjective scores after 8 months' treatment a significant difference ($P < 0.02$) was seen in 6 out of 7 variables, while in the objective scores all but 2 of the variables showed a significant difference in favour of SCG eyedrops ($P < 0.01$).

Clinical assessments made after 1 and 8 months' treatment of overall efficacy, patient's opinion, clinical response, and side effects showed that a high percentage of patients found the SCG eyedrops superior to Antistin-Privine for all the variables (Table 3). Only 1 report of stinging was reported for each treatment after 8 months.

Table 1 *Patient's characteristics*

Characteristics	Class or measure	Group I	Group II	Group III
Sex	Male	44	12	11
	Female	14	3	4
Age	Range	4-30	8-20	6-32
	Mean	14.1	12.8	14.8
Duration of condition (years)	Range	1-15	1-10	0-13
	Mean	3.5	5.6	3.9
Atopy	Yes	3	2	0
	No	55	13	15
Other conditions	Asthma	0	2	0
	Eczema	6	2	0
	Hayfever	0	2	0
	Rhinitis	3	2	0

Table 3 Changes in the symptoms and signs of VKC after treatment with A-P (right eye) and SCG (left eye) after eight months

Variable	Response	After 8 months		Significance
		Right eye A-P	Left eye SCG	
Efficacy	High	0	14	$P < 0.001$
	Mild/moderate	3	1	
	None	12	0	
Patient's opinion	Satisfactory	4	14	$P < 0.001$
	Unsatisfactory	11	1	
Did clinical condition improve?	Yes	4	14	$P < 0.001$
	No	11	1	
Side effects	Yes	0	0	Sample too small (0) $P = 1.0$
	No	15	15	
Stinging or irritation	Yes	2	2	$P = 1.0$
	No	13	13	

GROUP III

In this group 15 patients were given SCG to the left eye and Decadron to the right. The pattern of treatment and method of analysis were similar to that used for group II. All the patients in this group were classified as nonatopic, with no other allergic conditions (Table 1).

The subjective measurements recorded after 10 days and 1 and 8 months did not reveal a significant difference between the 2 treatments for any of the variables except stinging, where SCG eyedrops were found to sting significantly more than Decadron.

Comparison of the objective scores recorded after subsequent visits for the right and left eyes respectively showed that after 8 months' treatment both treatments performed equally for all the variables except 3, the exceptions being pigmentation, corneal vascularisation and ocular tension, which showed significant differences in favour of SCG eyedrops. In the case of ocular tension there was an increase in the eye given Decadron and a decrease in the eye given SCG.

Six right eyes out of 15 receiving Decadron showed an increase of ocular tension, with an average of $+0.9$ mmHg (Schiotz) after 1 month's treatment, and SCG-treated eyes showed no difference (Table 4).

Eight Decadron treated eyes showed an increase in ocular tension by an average of $+1.2$ mmHg after 8 months' treatment, and SCG treated eyes showed a decrease of an average of 0.2 mmHg (Table 4). After 1 year no further change of the tension was recorded.

The clinical assessments made after 1 and 8 months' treatment revealed an equivalent response from both treatments (Table 5).

In all these groups the results after 12 months' treatment were similar to those presented after 8 months.

Discussion

Fifty-eight patients were administered 2% SCG eyedrops as sole therapy, and after 8 months' treatment the efficacy was rated as high in 42 patients, moderate/mild in 13, and nil in 3. Such a response indicates that SCG may block an important element of type I hypersensitivity which is thought to exist in VKC.¹⁰ In some patients additional treatment with topical steroid was found necessary at the start of treatment or during acute exacerbations. Thus, 8 patients out of 88 received steroid therapy for 1 week at the start of the trial in the severe forms of the disease. However, since the overall steroid requirement was removed in many patients and considerably reduced in others, this has helped greatly to remove the unwanted side effects of topical steroid therapy in VKC, such as increased

Table 4 Differences between changes in ocular tension after 1 and 8 months

		Mean difference for		Significance
		Right eye (Decadron)	Left eye (SCG)	
Tension	After 1 month	0.9	0.0	$P < 0.01$
	After 8 months	1.2	-0.2	

Table 5 Changes in the symptoms and signs of VKC after treatment with Decadron (right eye) and SCG (left eye) after 1 and 8 months

Variable	Response	After 1 month		After 8 months	
		Right eye (Decadron)	Left eye (SCG)	Right eye (Decadron)	Left eye (SCG)
Efficacy	High	12	13	13	15
	Mild/moderate	2	2	1	0
	None	1	0	1	0
Patient's opinion	Satisfactory	14	15	14	15
	Unsatisfactory	1	0	1	0
Did clinical condition improve?	Yes	14	14	15	15
	No	1	1	0	0
Side effects	Yes	0	0	0	0
	No	15	15	15	15
Stinging	Yes	0	0	0	1
	No	15	15	15	14

intraocular pressure. As well as confirming the results of Easty *et al.*¹⁰ and Tabbara and Arafat¹¹ this study has established that SCG is effective in nonatopic patients with a minimum of other allergic diseases. However, these results are in contrast to that reported by Hyams *et al.*,¹³ who failed to show a positive response with SCG in patients without a history of allergy.

When SCG eyedrops were administered to the left eye and Antistin-Privine eyedrops to the right in 15 patients, a significant number of the patients preferred the SCG eyedrops. After 8 months' treatment the clinical condition was found to improve in 14 (93%) on SCG therapy, while only 3 (20%) responded to Antistin-Privine. In spite of the presence of a vasoconstrictor in Antistin-Privine a rebound phenomenon occurred, and reflex vasodilatation was evident after instillation of the drops, which caused discomfort to the patients. Pigmentation was increased after SCG therapy, but no such changes were detected after Antistin-Privine therapy. No change in the ocular tension was observed in either the SCG or Antistin-Privine treated eyes.

When SCG eyedrops were administered to the left eye and Decadron to the right in 15 patients, both treatments were found to give equivalent clinical responses. However, the one important exception was ocular tension, which after 1 month's treatment was found to have increased by 0.9 mmHg in Decadron treated eyes, while SCG treated eyes showed no difference. After 8 months' treatment with SCG a decrease of 0.2 mmHg was recorded, while with Decadron it was increased by 1.2 mmHg. As regards transient stinging, this was a constant feature in the SCG treated eyes but not with Decadron.

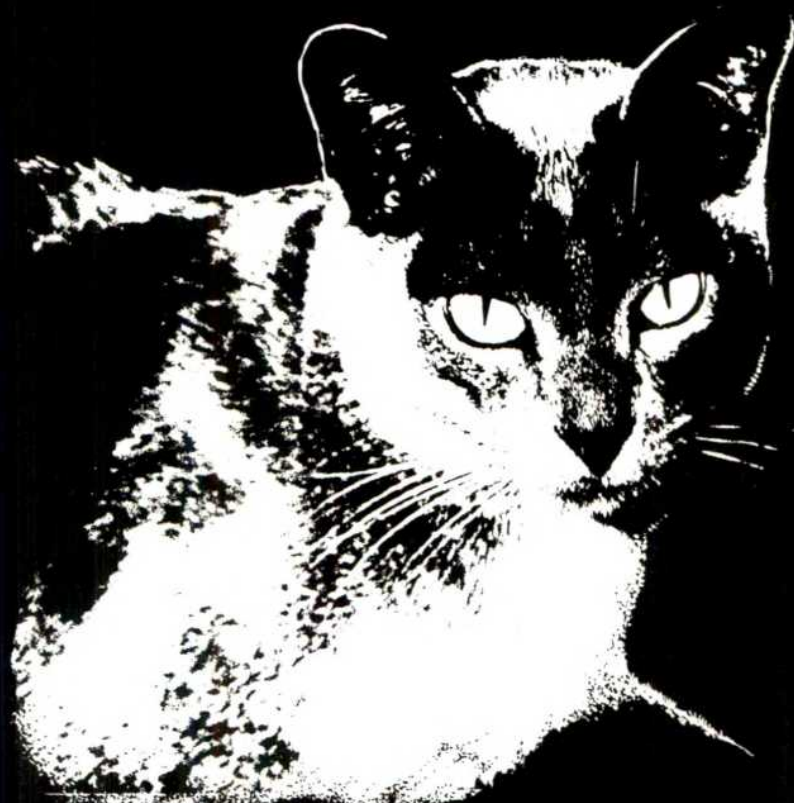
In conclusion, this open assessment study has shown that 2% sodium cromoglycate eyedrops are an effective treatment in a high percentage of patients with VKC. Marked improvement was recorded in mild and moderate cases, though in severe cases or in acute exacerbation additional

steroid therapy was recommended. Although stinging did occur, the eyedrops were free from important side effects, in particular from the rise in ocular tension found with steroid eyedrops. In steroid-induced glaucoma SCG eyedrops decrease the ocular tension when replacing steroid therapy in VKC. In a within-patient comparison study SCG eyedrops were equal to Decadron and superior to Antistin-Privine with regard to efficacy.

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Echo 11 conjunctivitis

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SUMMARY We describe a case of Echo 11 virus infection producing a moderately severe conjunctivitis in a laboratory worker who had handled infected material. This virus has previously been known to cause systemic disease, sometimes fatal, in children.

Many viruses can cause conjunctivitis, but identification of the causative virus has therapeutic implications in only a small number of cases. However, the epidemiological consequences can sometimes be important.

We report a case of Echo 11 viral conjunctivitis without systemic symptoms in a laboratory technician who had handled infected material. This endemic virus is usually associated with aseptic meningitis and gastrointestinal or respiratory illnesses in infants, and can be fatal.¹ The only other reported case of this virus producing a conjunctivitis was also in a laboratory worker,² and there is evidence that infection is spread by the droplet and contact routes with an incubation period of a few days.³

Case report

A 23-year-old medical laboratory scientific officer was seen on 14 December 1978 complaining of redness, soreness, and stickiness of both eyes on waking that morning. She had no previous ophthalmological complaints, but 5 days previously had had an upper respiratory infection which persisted for 2-3 days. Three days before the onset of her eye symptoms she had been handling material which was later shown to be infected with Echo type 11 virus.

On examination her visual acuity was 6/5 in both eyes. There was a purulent watery discharge from both eyes and mild conjunctival injection. Both upper tarsal conjunctivae were covered with a papillary reaction and fresh moderate sized follicles. The lower tarsal conjunctiva had fewer follicles and papillae and some small haemorrhages. There was

no keratitis, and the right preauricular gland was enlarged.

She was treated with chloramphenicol drops to both eyes, and 4 days later she had improved considerably. The haemorrhages had absorbed, there were fewer follicles, and more papillae had appeared on the upper tarsal conjunctivae. By 4 January 1979 the patient was symptom-free. There were a few remaining follicles and papillae on the tarsal conjunctivae, but at no stage did the patient develop any keratitis.

INVESTIGATIONS

The haemoglobin and white cell counts were normal at the onset of her illness.

At presentation conjunctival swabs were collected in virus transport medium and immediately inoculated into primary cynomolgus monkey kidney (CMK), human embryonic lung fibroblasts, and HeLa cell cultures at 37°C. The following day a cytopathic effect was noticed in the human lung fibroblast cultures, and the material was passaged into CMK culture, where 3 days later an enterovirus-like cytopathic effect was seen. Electron microscopy (after centrifuging at 100 000 *g* for 30 minutes) showed small round virus particles (Fig. 1). An Echo 11 virus was identified from the cell culture by neutralisation with specific antisera.

Serum taken at the onset of the illness and 3 weeks later showed a significant rise in neutralising antibody titre from 1:20 to 1:80 against Echo 11.

Discussion

Viral isolation and serological studies confirmed that the patient experienced an Echo 11 virus conjunctivitis. Three days before her illness she had handled material infected with the same virus, and this was probably the source of her infection. The

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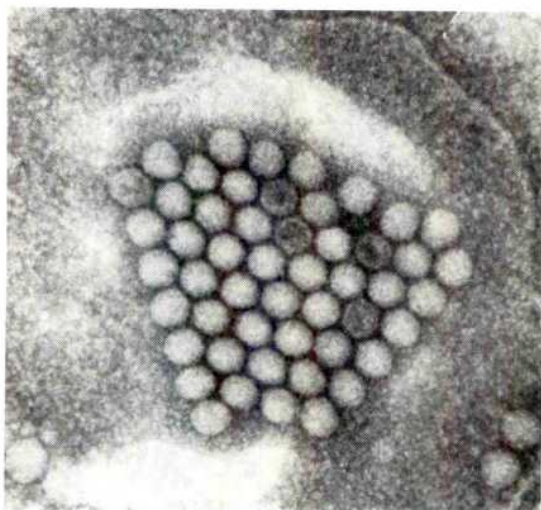


Fig 1 Echo 11 virus particles from the patient ($\times 193\,000$).

initial ocular symptoms were moderately severe, but the infection resolved rapidly on nonspecific treatment with no further ocular consequences.

Echo viruses form part of the enterovirus group, the other main subtypes being the polio and Coxsackie groups. Because of the importance of the polio viruses much work has been done on the epidemiology of this group and their associated diseases. Occasionally other enteroviruses such as Coxsackie B2² and Echo 7¹ have been reported to cause conjunctivitis. However, two pandemics of enterovirus infection have occurred. The first in Singapore in 1970 was caused by Coxsackie A24,⁵ and later acute haemorrhagic conjunctivitis was shown to be caused by enterovirus 70.⁶

Many Echo 11 infections are subclinical, but the diseases it usually produces are aseptic meningitis and gastrointestinal or respiratory illness. Echo 11 infections are not uncommon. There appears to be a high incidence in 2 successive years, occurring in a

5-year cycle. In 33 weeks of 1978, 445 infections were reported; most of them were in children of under 4 years of age, and 9 children died.⁷ An epidemic of Echo 11 infection in a baby unit killed 3 neonates of 9 infected; infection was thought to be spread by droplet and hand contact.³

The identification of viruses that produce conjunctivitis remains a problem. Positive cultures are obtained only from a small percentage of cases that are likely to have a viral origin, and it is usually impossible to identify the causative virus from the clinical appearance of the conjunctiva. The various adenovirus subtypes and herpes simplex are the commonest viruses isolated, but enteroviruses are widely distributed and some types are known to produce conjunctivitis. Whether or not they play any significant role in endemic viral conjunctivitis is unknown. It might be important to recognise that conjunctivitis can be the only manifestation of infection with Echo 11 virus and that there might therefore be a risk to small children from those involved in their care and handling if they were so infected.

We thank Professor J. E. Banatvala for his assistance.

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An outbreak of adenovirus type 4 conjunctivitis

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SUMMARY An unusually large outbreak of conjunctivitis caused by adenovirus type 4 involved 113 proved cases during a 7-month period. Though the disease was less severe than is commonly seen in epidemic keratoconjunctivitis caused by other serotypes, the cornea was affected in 23% of cases and symptoms persisted for at least 5 weeks in 6 patients. A concurrent increase in nonocular adenovirus type 4 infections in the Bristol area was not observed. Nine of the cases could have arisen as a result of hospital cross-infection.

Of the 35 distinct serological types of adenovirus only a few are commonly associated with conjunctivitis in temperate regions. Types 3 and 7 are recognised as the principal causes of 'swimming pool' conjunctivitis and pharyngoconjunctival fever.^{1,2} Types 8 and 19 typically cause the more severe epidemic keratoconjunctivitis.³⁻⁵ Type 4 and less frequently type 7 give rise to respiratory infections, which may occur in epidemic form, typically among military recruits, being referred to as acute respiratory disease.⁶ Type 4 conjunctival infections are uncommon in the civilian population and have usually been reported as isolated or small numbers of cases during outbreaks caused by other serotypes,⁷ although an outbreak of pharyngoconjunctival fever caused by adenovirus type 4 has occurred in relation to a contaminated swimming pool.⁸

A recent outbreak of adenovirus type 4 conjunctivitis in Bristol involving a large number of persons provided an opportunity to study the range of ocular manifestations resulting from infection with this serotype and to compare it with that previously reported for other adenoviruses.

Materials and methods

Patients presenting with signs and/or symptoms of possible viral conjunctivitis were seen at the Bristol Eye Hospital Casualty Department. Examination included detailed slit-lamp microscopy and swabs were taken for bacteriological and virological culture.

All swabs for virology were transported in milk saline transport medium and reached the laboratory

within 12 hours. They were examined, as previously described⁹ in cultures of Hep-2 and human embryo diploid fibroblasts, and some were also cultured for TRIC agent.

Serum samples were not taken because the detection of type 4 antibody, especially in single specimens, does not have the same significance as the presence of specific antibody in type 8, 10, or 19 eye infections in temperate climates.

Results

During the 7-month period from the beginning of March to the end of September 1978, 640 swabs for virus culture were taken from the eyes of patients with possible viral conjunctivitis. These patients all came from the population of approximately 1 million people served by the Bristol Eye Hospital.

Adenovirus type 4 was isolated from eye swabs from 113 of these patients (Fig. 1). The sexes were almost equally affected, with 59 females and 54 males contributing to the total. The average age of the affected patients was 29 years, range 3 months to 67 years. During the same period 22 strains of other adenoviruses were isolated from similar cases. Two belonged to type 1, 5 to type 3, 1 to type 13/30, and 14 to type 7, which indicated that a minor concurrent outbreak with the last serotype had occurred.

Of the 113 proved adenovirus cases of type 4 infection swabs had been taken from 10 for isolation of the TRIC agent and from 95 for bacteriology. The results of these investigations were negative except for those from 1 child of 9 months, who yielded a pneumococcus in addition to adenovirus type 4.

In 9 instances infection could possibly have been

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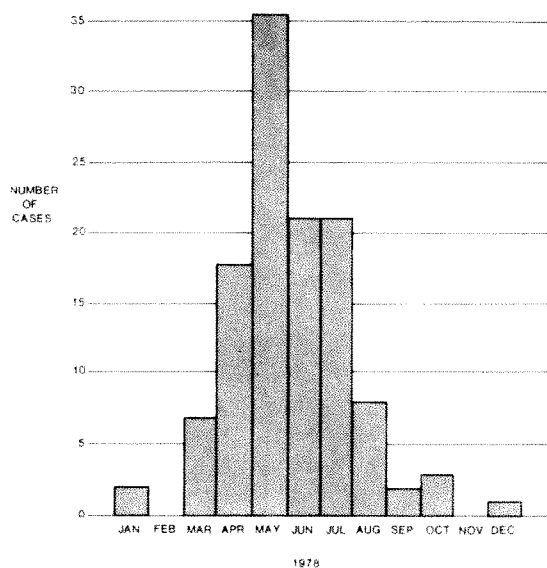


Fig. 1 Distribution of cases during 1978.

acquired in hospital. In these cases patients developed symptoms of conjunctivitis a week or so after attending the outpatients department for some other condition. Five of the patients initially attended with a foreign body in their eye. Three had the foreign body removed by the casualty officer (for further details of 1 see case report below) and 2 by nursing staff. Another 2 patients had irrigation of their tear ducts, also in the treatment room. A further patient, who was responding to treatment for a bacterial periorbital cellulitis, developed a conjunctivitis subsequently shown to be caused by adenovirus type 4. The remaining case of cross-infection was in a casualty officer. In addition a further 15 patients gave a history of close contact with another person with symptoms of conjunctivitis, 4 of whom were also proved cases attending the Bristol Eye Hospital.

During the period that the 113 isolates of adenovirus type 4 were made from eyes the combined isolations of this serotype by the hospital and the public health laboratories, serving the Bristol area, from sites other than the eye numbered only 3. The corresponding figures for adenovirus type 7 were 14 strains from the eye and 14 strains from other sites (S. K. R. Clarke, personal communication).

SYMPTOMS (109 INFECTIONS)

Most of the patients presented complaining of soreness and watering of one eye and only a few with a foreign body sensation. The duration of

symptoms at the time of presentation ranged from a few hours to 10 days (average 3 days). Symptoms persisted for 14 days on average and ranged from 7 to 42 days. Thirty-four patients progressed to bilateral disease, all within 5 days of onset of symptoms, which in the contralateral eye were typically less severe, though in 8 instances the 2 eyes were equally affected. Fourteen patients (12%) had concurrent respiratory symptoms, and 1 was sufficiently ill to be referred to the medical outpatients department (see case report below). Two patients complained of blurring of vision related to corneal opacities.

SIGNS

The frequencies of the various ocular signs are recorded in Table 1. The predominant finding was a follicular conjunctivitis of the lower tarsal conjunctiva. A total of 26 patients had evidence of corneal involvement. Nine of 14 patients with punctate epithelial keratitis did not develop subepithelial lesions; while 12 out of 17 patients who had subepithelial lesions were not observed to have had punctate epithelial keratitis. Corneal subepithelial opacities (Fig. 2) appeared between 3 and 35 days (average 11 days) after the onset of symptoms and had resolved in all but 2 cases after a further 7 to 35 days (average 12 days).

Two patients developed a dendriform epithelial defect early in the course of the infection and went on to develop discrete stromal opacities. Herpes simplex virus was not isolated from either affected eye. One of these patients, a 67-year-old woman, was seen 6 months later, and, although she was asymptomatic, several faint immediately subepithelial opacities were seen in the upper segment of the cornea. This type and distribution of opacities has

Table 1 Distribution and frequency of signs during the course of adenovirus type 4 infections in 109 patients

Site	Sign	No. (and %) of patients in whom present
Lids	Lid swelling	20 (18)
	Conjunctival hyperaemia	109 (100)
	Follicles	91 (83)
Conjunctiva	Papillae	52 (48)
	Chemosis	13 (12)
	Haemorrhage	9 (8)
	Membrane	3 (3)
Cornea	Punctate epithelial keratitis	14 (13)
	Subepithelial opacities	17 (16)
Regional glands	Lymphadenopathy	23 (21)

been described in the later follow-up of an adenovirus type 10/19 infection.⁹

With the exception of one slowly resolving large plical haemorrhage, all haemorrhages were petechial,

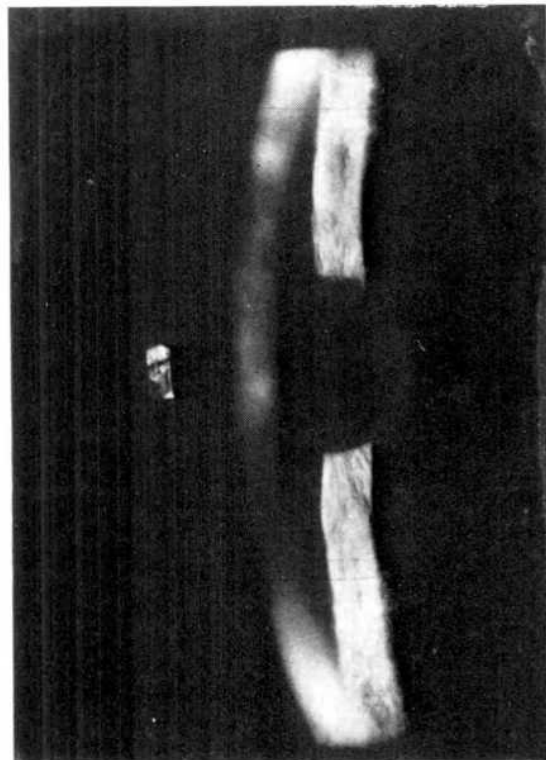


Fig. 2 Slit-lamp photograph showing subepithelial opacities.

mainly in the upper tarsal conjunctiva (Fig. 3) and typically lasted for only 2 to 3 days.

CASE REPORT

A 19-year-old male student presented with a foreign body sensation in the left eye of several hours' duration. An eyelash was removed from under the upper lid. Seven days later he returned giving a 3-day history of his left eye being sore and sticky. Hourly antibiotic drops from his general practitioner had failed to produce any improvement. On examination he was seen to have a marked follicular conjunctivitis with a punctate epithelial keratitis accompanied by a preauricular lymphadenopathy. Eye swabs taken at that time yielded an adenovirus type 4; bacterial and chlamydial cultures were negative. On the fourth day of illness he felt feverish and developed a dry cough. He was referred to the medical outpatients department, where a diagnosis of acute bronchitis was made. He was treated with oral tetracycline. Two days later the pain and stickiness of the eye were much less, and examination revealed a chemotic conjunctiva and a clear cornea. Two weeks after onset he felt better and his cough had lessened. On this occasion several subepithelial opacities were noted in his left eye, which were seen to be clearing after a further week, at which time he was asymptomatic.

When seen after 8 months he was well, but examination of the cornea revealed 2 small discrete central subepithelial opacities and 1 similar lesion in the superior peripheral cornea. He was aware of a vague distortion of vision in this eye, though visual acuity was 6/4.



Fig. 3 Petechial haemorrhages in the upper tarsal conjunctiva.

Discussion

This outbreak of adenovirus type 4 conjunctivitis was far larger than any previously reported, and the number of strains isolated from eyes, 113, during the 7-month period greatly exceeded the total number of isolates, 34, of this virus from all sites made by the local hospital and public health laboratories over the whole of the preceding 6 years. The apparent low frequency of concurrent adenovirus type 4 infections of the respiratory tract, only 3 isolations from all other sites, could have resulted from biased sampling. However, adenovirus type 7 was isolated with equal frequency from eyes and other sites, 14 strains from each, during the same period. This would indicate that this strain of adenovirus type 4 did have a true predilection for the eye. This situation appears to have been peculiar to the Bristol area in as much as 113 of the 118 isolations of adenovirus type 4 in the Bristol area during a 9-month period were associated with conjunctivitis, but only 67 of the 150 isolates reported to the Communicable Disease Surveillance Centre (CDSC) from the remaining laboratories in England and Wales were from ocular infections.¹⁰ In summary, 40% of all adenovirus type 4 infections reported to the CDSC during the first 9 months of 1978 occurred in the Bristol area, as did 63% of all reported cases of conjunctivitis caused by this serotype.

The 9 instances of probable hospital cross-infection illustrate that it is possible for transmission of the virus to occur by examination alone and that the trauma of a procedure to the eye, for example, removal of a foreign body, increases the likelihood. Unlike the outbreak of adenovirus type 4 PCF related to a swimming pool,⁸ the geographical distribution of cases, excluding the small number of presumed hospital cross-infections, showed no clustering. Furthermore, the typical history was of spontaneous onset, and only 15 (13%) patients gave a history of contact with another person with signs and symptoms of conjunctivitis. This suggests that close contact with an infected eye is not a prerequisite for transmission of the virus. The possibility of asymptomatic ocular carriage acting as a reservoir of adenovirus infection has been raised with type 19.⁵ However, asymptomatic respiratory carriage would provide even greater opportunity for the dissemination of virus and is more likely to occur with adenovirus type 4, which commonly infects the respiratory tract. However, if asymptomatic carriage was a major factor in the epidemiology of the outbreak it would be necessary to postulate that this particular strain had a greater affinity or pathogenicity for the conjunctiva than

previously circulating strains of adenovirus type 4.

Detailed descriptions of the clinical features of adenovirus type 4 conjunctival infections are scanty, but it has been thought that corneal involvement is rare. Only 1 instance of superficial punctate keratitis occurred in 15 patients with adenovirus type 4 conjunctivitis in Taiwan.⁷ No corneal involvement was observed in a further 20 infections seen during an outbreak of haemorrhagic and follicular conjunctivitis in Rome.¹¹ The observation of petechial haemorrhages in adenovirus conjunctivitis serves as a reminder that acute haemorrhagic conjunctivitis is not pathognomonic of enterovirus infection.

Adenoviruses may be classified according to their haemagglutination properties.¹² The epidemic types, 8, 10, and 19, belong to group 2; they are transmitted from eye to eye and frequently give rise to corneal opacities which commonly persist for many months. Type 4 adenovirus belongs to another group and behaves somewhat differently. There was no evidence that eye to eye was the common mode of spread of this serotype. The incidence of subepithelial opacities was only 15%, and in all but 2 cases they have resolved within 32 days of their appearance. This is considerably less than the corresponding figures for outbreaks caused by type 8 (82%)³ and type 10/19 (58%),⁹ which have occurred previously in this region. However, this strain of adenovirus type 4 itself behaved atypically by causing disease in which ocular features predominated.

We are grateful to the staff of the Eye Hospital Casualty Department for collection of swabs and to the staff of the Bristol Royal Infirmary Virus Laboratory for the study of specimens for virus isolation.

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Allergic conjunctival granulomas

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SUMMARY Seven cases are reported from Australia of benign granulomas of the conjunctiva occurring principally in children. Conjunctival granulomas of this kind have not previously been recorded in Australia. Both clinically and histologically they are identical to those described by Ashton and Cook¹ as allergic granulomas of the conjunctiva exhibiting the Splendore-Hoepli phenomenon.

Seven cases of a rare type of conjunctival granuloma have come to our notice in Australia over a period of 15 years.

Patients and methods

The patients ranged in age from 4 to 26 years, and 5 of them were under 11 years; there were 2 females and 5 males. They suffered mild conjunctival hyperaemia and irritation and slight discharge from one or both eyes for a week or two before presenting. The granulomatous lesions consisted of 1 or more raised yellow nodules immediately beneath the epithelium of the bulbar conjunctiva (Fig. 1). In the absence of surgical intervention the lesions disappeared spontaneously within a few weeks or months of onset. In 1 of the 7 cases similar

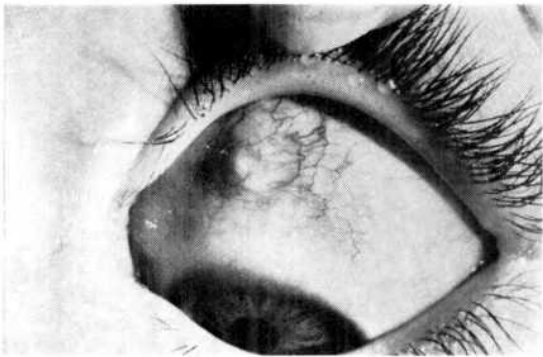


Fig. 1 Typical appearance of granulomas in the bulbar conjunctiva.

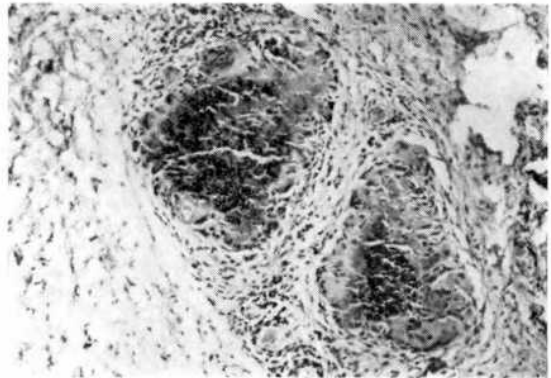


Fig. 2 Photomicrograph of the characteristic granulomatous foci showing nuclear debris and amorphous substance surrounded by epithelioid cells and giant cells (H and E, $\times 200$).

lesions appeared in the contralateral eye 12 months later. The patients were otherwise quite well, and their chest x-rays, blood counts, and erythrocyte sedimentation rates were normal. In the only case so tested the Mantoux reaction was negative.

PATHOLOGY

Sections of the nodules in all the cases showed 1 or more granulomatous inflammatory foci consisting of amorphous eosinophilic material and nuclear debris, closely surrounded by epithelioid cells, giant cells, and eosinophils (Fig. 2). In some instances the epithelioid cells had assumed an elongated form and arranged themselves in a palisade. No foreign bodies, parasites, or organisms of any kind were identified in any of the lesions, and cultures consistently proved negative.

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Discussion

The granulomas are similar in every way to those described by Ashton and Cook¹ as allergic granulomatous nodules of the conjunctiva showing the Splendore-Hoepli phenomenon. These authors record that the eponym derives from Splendore's first description in 1908 of eosinophilic granulomas around fungal spores and Hoepli's subsequent report of identical reactions around schistosoma eggs. In the 20 conjunctival granulomas painstakingly investigated by Ashton and Cook no ova or spores were found, but 2 granulomas contained

fragments of nematode cuticle. Transmission electron microscopy performed on some of the 20 granulomas revealed abundant amorphous substance thought to be antigen-antibody complex.

We are grateful to Drs Justin Murphy, J. Cairns, P. J. Lewis, J. Roache, C. G. Cullity, and Mark Harrison, who referred cases, and to the Medical Illustration Department of the Royal Victorian Eye and Ear Hospital for help in preparing the photographs.

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Late complications of pterygium treatment

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SUMMARY Long-term complications of pterygium excision and beta irradiation in 63 eyes of 57 patients are described. The age of the patients at treatment ranged from 27 to 69 years (mean 48 ± 11), and complications were assessed 3 to 20 years later (mean 12 ± 3). The pterygia were excised, leaving bare sclera, and beta irradiation of total dose 750 to 5200 rads (mean 3475 ± 916) was given, except in 7 patients who had repeated courses or overlapping fields of beta irradiation. Scleral ulceration was present in 51 eyes and sectorial lens opacities with normal visual acuity (VA) in 19 eyes. Radiation induced cataract occurred in 3 eyes, with reduced vision. Ptosis, symblepharon, and iris atrophy were also seen. Pseudomonas endophthalmitis occurred in 4 patients with scleral ulceration. Beta irradiation to prevent recurrence of pterygia is a significant cause of iatrogenic ocular disease. There is a need to modify the beta irradiation dosimetry at present in use.

Pterygium excision is a common ophthalmic operation that is often considered trivial, but without conjunctival radiotherapy recurrence rates may be as high as 69%, especially in the hot, dry, sunny environments of Australia¹ and the Middle East.² Numerous surgical modifications to simple excision have been reported, but none are notably advantageous.² Beta irradiation after excision reduced the recurrence rate to a range of 0.5%³ to 16%.¹ Apart from local steroids, artificial tears, and dark glasses postoperatively, the only alternative treatment is topical thiotepe. Although reported to be as effective as radiotherapy,⁴ thiotepe has not been widely accepted.

Pterygium recurrence rates have often been reported, but late complications of pterygium treatment have received little emphasis. Fifty-seven patients with late complications are presented and their relationship to beta irradiation discussed.

Patients and methods

Patients with conjunctival, corneal, or scleral complications from previous pterygium treatment were obtained on request from other ophthalmologists and by a search of the records of 3 teaching hospitals. Four new cases presented at hospital clinics during the study. All but 5 patients were

examined by one of us (K.H.T.). Adequate records and photographs for inclusion in parts of the study were available on these 5.

Details of pterygium treatment, the course of ocular symptomatology, corrected visual acuities (VA), biomicroscopic measurement of avascular conjunctival patches, size of scleral ulceration and distance from the limbus, the position and assessment of ulcer depth, colour, and presence of overlying tissue were recorded. In addition telangiectatic vessels were noted, and after pupillary dilatation lens opacities were drawn and graded. The tear meniscus, break-up time, and results of an unstimulated Schirmer's test were recorded together with fluorescein and rose Bengal staining. Any other ocular pathology was noted and an external photograph was taken. Radiotherapy records with complete details of treatment were available in all but 2 patients. Of the 57 patients examined, 46 (51 eyes) had scleral ulceration, 2 had corneal ulceration, and 9 (10 eyes) had pathology confined mainly to the conjunctiva. The age of initial pterygium treatment with excision and beta irradiation ranged from 27 to 69 (mean $48 \pm (\text{SD}) 11$). Examination took place 3 to 20 years later (mean 12 ± 3). There were 32 males and 25 females, of whom 1 was aboriginal and the rest were European.

Pterygium excision leaving bare sclera was used in all patients. In 15 eyes recurrent pterygia had been re-excised, and 8 of these had previously had beta irradiation (Table 1). Beta irradiation was repeated in 5 eyes and involved overlapping fields in 2 other

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Table 1 Summary of pterygium treatment in 57 patients with late complications: treatment is outlined for eyes with corneal or scleral ulceration, with surface pathology without ulceration, and for fellow eyes

	Treatment							
	$E_1 + \beta_1$	E_1 $E_1 + \beta_1$	E_1, E_2 E_2 $E_2 + \beta_1$	$E_1 + \beta_1$ E_2	$E_1 + \beta_1$ $E_2 + \beta_2$ $E_2 E_4$	E_1 $E_2 + \beta_2$ $E_2 + \beta_2$	$E_1 + \beta_1$ $E_2 + \beta_2$	E only
Ulcerated	45*	2	1	0	1	2	2	0
Surface pathology only	7	2	0	1	0	0	0	0
Fellow eyes	9	1	1	1	0	0	1	5

E=excision; β =beta irradiation; subscript indicates sequence of E and β respectively. *Includes 2 corneal ulcers.

Table 2 Late complications of pterygium treatment: summary of patients with repeated or overlapping fields of beta irradiation

Beta irradiation treatment	Total dose (rads)	Age at initial irradiation*	Years of follow-up	Visual acuity	Lens opacity	External eye appearance
1. 3600 r over 2 weeks repeated 2 years later Fellow eye	7200 —	57 —	13	3/60 6/6	Dense cataract Minimal	Deep scleral ulcer Normal
2. 4500 r over 2 weeks, 5 yr later 2300 r over 1 week Fellow eye	6800 —	28 —	15	6/6 6/5	Sectorial Nil	Deep scleral ulcer Normal
3. 3000 r over 2 weeks repeated 7 years later Fellow eye, only initial 3000 r	6000 3000	44 44	19 19	6/6 6/6	Sectorial Nil	Deep scleral ulcer Normal
4. 3600 r over 2 weeks, 1 yr later 2300 r Fellow eye, only initial 3600 r	5900 3600	45 45	13 13	6/36 6/5	Sectorial Nil	Moderately deep scleral ulcer Recurrent pterygium
5. To both eyes: 4000 r over 5 weeks 10 months later, 2400 r to each of 2 overlapping fields	6400 (8800)	48	15	6/6 6/6	Nil Nil	Full thickness vertical linear defect, uveal prolapse, covered by conjunctiva (Fig. 5) Normal
6. 4000 r over 1 week, then at 1 month, 1300 r to each of 2 overlapping fields Fellow eye, 2400 r over 2 weeks	5300 (6600) 2400	30 37	12 5	6/5 6/4	Sectorial Nil	Moderately deep scleral ulcer Normal
7. 3200 r over 3 weeks to 2 overlapping fields Fellow eye	3200 (6400) —	56 —	14	6/4 6/4	Nil Nil	Deep scleral ulcer Normal

*In years; r=rads.

eyes (Table 2). Beta irradiation was started within the first week after excision in 55 eyes (87%). Twice as many were treated during winter as during summer. All but 2 eyes had fractionated treatment (Table 3). Two strontium-90 applicators were used. One was a 1.5 cm circular plaque with an emission rate of 8.7 rads s^{-1} when supplied in 1962. The other was an ellipse with active surface dimensions of 13×18 mm and an emission rate of 15.3 rads s^{-1} in 1966. For the 3-year periods of 1970–2, 1973–5, 1976–8, 1470, 4525 and 4864 patients respectively had beta irradiation after pterygium excision in Perth.

Results

SYMPTOMATOLOGY

On examination ocular pain or irritation, epiphora, and photophobia were severe in 15 (26%) of the patients with ulceration and in 2 of 9 patients referred with mainly conjunctival abnormalities. Symptoms were absent in 12 patients (21%). These symptoms had been present from the time of initial pterygium treatment in 24 patients (42%). Severe ocular pain and photophobia during or immediately following beta irradiation was present in 18 (32%).

Table 3 *Late complications of pterygium treatment: fractionation and dosage* of initial beta irradiation*

	<i>Single dose at operation</i>	<i>3 doses over <1 week</i>	<i>3 doses over 2 weeks</i>	<i>1 doses over 3 weeks</i>	<i>1 or 3 doses over 1 weeks</i>
<i>Ulcerated†</i>					
number	1	15	27	3	4
dose range	750	2100-5100	2400-5100	3200-5200	4000-5300
mean	—	3135	3350	4400	4475
<i>Surface pathology</i>					
number	1	2	7	0	0
dose range	2200	4500	2400-4800		
mean	—	each	2700		
<i>Fellow eyes</i>					
number	0	3	8	1	1
dose range		2600-4500	2400-4000	4800	4000
mean		3433	3125	—	—

*In rads; †2 unknown.

Table 4 *Patients with severe visual loss or aphakia*

<i>Age at treatment</i>	<i>Years of follow-up</i>	<i>Visual acuity</i>	<i>Radiation dose*</i>	<i>Ocular pathology</i>
1. 45	13	6/36 6/5	3600-2300 1 yr later 3600 only	Marked posterior sectorial and anterior crescentic opacity Moderately deep scleral ulcer Normal
2. 52	11	6/6 6/5	4500 Nil	Aphakic (8 yr after treatment) Deep scleral ulcer Normal
3. 57	13	3/60 6/6	3600-3600 1 yr later Nil	Marked posterior sectorial and anterior cortical opacities Deep scleral ulcer Minimal wedge opacities
4. 60	13	6/9 Nil	3600 Nil	Aphakic (12 yr after treatment) Deep scleral ulcer Enucleated (trauma)
5. 55	11	3/CF 6/12	3900 3900	Aphakic (8 yr after treatment) Deep scleral ulcer Aphakic and deep scleral ulcer
6. 65	12	6/12 6/12	2700 Nil	Aphakic (8 yr after treatment) Deep scleral ulcer Aphakic (9 yr after treatment) No ulceration
7. 69	11	6/36 6/24	3000 Nil	Aphakic (5 yr after treatment) Deep scleral ulcer Aphakic (6 yr after treatment) No ulceration
8. 69	12	3/CF 6/18	4500 4500	Dense cataract, deep scleral ulcer Aphakic (8 yr after treatment)
9. 65	9	6/HM 6/18	2400 2400	Posterior polar cataract Moderately deep scleral ulcer Posterior polar cataract
10. 55	3	Nil 6/12	2400 2400	Deep scleral ulcer Pseudomonas endophthalmitis Eviscerated No lens opacity Deep scleral ulcer
11. 53	11	Nil 6/6	2800 Nil	Deep scleral ulcer Pseudomonas endophthalmitis Eviscerated Normal

*In rads given as 3 doses over 2 weeks except the 2300 given as a single dose. CF=count fingers; HM=hand movements.

Table 5 Clinical details of patients with scleral or conjunctival complications after pterygium treatment excluding repeated or overlapping fields of beta irradiation*

External pathology	Age at initial treatment (no.)	Years of follow-up	Total dose of irradiation	Ulcer size† (no.)
Superficial ulceration	40±11 (6)	12±3	3710±1415	5.1±4.7 (5)
Moderately deep ulcer	52±10 (11)	11±3	3183±771	5.4±3.4 (10)
Deep ulceration	49±10 (26)	12±3	3507±891	6.3±3.6 (25)
Surface pathology only	42±11 (9)	9.5±4	3111±1121	—

*In rads; †6 unknown.

Reduced vision was a major complaint in 6 patients (10%) (Table 4). Four patients (7%) presented with an acute red eye of which two had pseudomonas endophthalmitis.

SCLERAL ULCERATION

Scleral ulceration occurred in 51 eyes of 46 patients. Five patients had bilateral ulceration and 1 had a nasal and a temporal ulcer on the one eye. Clinically ulceration was classified into 3 grades. Superficial ulceration was characterised by exposed sclera with an irregular white surface and shallow ulceration less than one-third scleral thickness (6 eyes) (Fig. 1). Moderate ulceration was characterised by a depth of one-third to two-thirds scleral thickness and a white base (14 eyes) (Fig. 2). Deep ulceration was characterised by a depth of two-thirds or greater with a dark base (31 eyes with 32 ulcers) (Fig. 3). Often only a thin layer of scleral fibres covered uveal tissue. In all 3 groups frequency and severity of symptoms were similar. There was no significant difference between the groups with respect to age at treatment ($P<0.1$), follow-up time ($P<0.3$), or total irradiation dosage when retreated cases were excluded ($P<0.2$) (Table 5).

The typical ulcer was 2–3 mm in diameter, had a corneal edge 1–2 mm from the limbus and was centred within half a clock hour of the horizontal meridian (Fig. 3). The ulcer usually had steep edges surrounded by very white avascular sclera, which was usually bare, and avascular conjunctiva with telangiectasia. The area of ulceration varied from 2.5 mm² to 16 mm² (mean 6.2 ± 3.7 mm²). There was no correlation between area and ulcer depth (Table 5). The centre of ulceration was more than 1 clock hour from the horizontal meridian in 9 eyes (17%). Seven (13%) were inferiorly situated (Figs. 2 and 4). It was often difficult to ascertain whether the sclera was completely bare of any tissue. A thin transparent layer of tissue was present in 11 eyes (21%) on careful biomicroscopy with cobalt blue light. Four (7%) had a documented history of persistent bare sclera with punctate rose Bengal

staining and failure of conjunctival regrowth after initial treatment for 1 to 7 years before ulceration developed. In 3 eyes a row of 2–4 translucent small spots were present. These were separate spots equidistant from the limbus by 1.5 to 2 mm, in line with the scleral ulcer. From 2 of these a small (0.5 mm) vascular tuft arose. This was not connected to surrounding surface vessels. Similar tufts were seen within the bare area unassociated with translucent spots in a few other eyes. A small encrustation occurred on the adjacent conjunctiva or in the ulcer bed in 10 eyes (20%). This was rough, hard, and stained with fluorescein and rose Bengal. An analysis revealed calcium and other crystals which were birefringent negative to a red plate compensator, suggesting urate. Episcleral vessels partially covered the ulcer base in 13 eyes (25%). In 4 eyes previous photographs revealed minimal vessel extension over 2 to 6 years. Telangiectasia surrounded the bare sclera in 48 eyes (92%) and was severe and cosmetically unacceptable in 18 (34%).

Two scleral ulcers were atypical. One was a small 1.5 mm diameter punched-out moderately deep ulcer covered by mildly abnormal conjunctiva. It developed 10 years after excision and a single dose of 750 rads. The other was a vertical curvilinear full-thickness scleral defect with a knuckle of uveal tissue covered by avascular and telangiectatic conjunctiva (Fig. 5). It was noted on routine examination 12 years after repeated excision and beta irradiation. Both eyes were treated, initially with 4000 rads over 2 weeks, then 10 months later a further 2400 rads was given to 2 overlapping fields. The scleral slit was perpendicular to the axis of the overlap. The fellow eye had white avascular sclera covered by avascular conjunctiva with surrounding telangiectatic vessels.

SURFACE PATHOLOGY IN EYES WITHOUT ULCERATION

Ten eyes of 9 patients had no ulceration and pathology mainly confined to the conjunctiva. This group did not significantly differ from those with

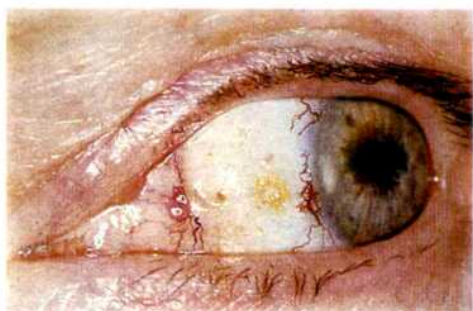


Fig. 1



Fig. 2



Fig. 3



Fig. 4



Fig. 5

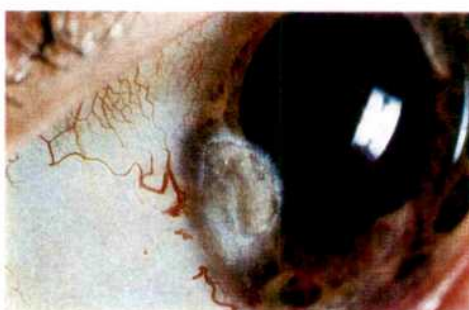


Fig. 6



Fig. 7



Fig. 8

ulceration with respect to age ($P < 0.1$), follow-up ($P < 0.1$), or total dose of beta irradiation ($P < 0.2$) (Table 5). When analysed in combination with the superficial scleral group, the lesser affected patients were significantly younger than patients with deeper ulceration ($P < 0.01$). Conjunctival pathology consisted of severe telangiectasia in 6 eyes (60%) and thinned avascular conjunctiva of area 3 to 18 mm (mean 9 mm) with an adherent encrustation in 3 (30%). Three (30%) had recurrent pterygia. The underlying sclera had a very white appearance in 8 (80%).

FELLOW EYES

Thirteen patients with unilateral ulceration had fellow eyes with previous pterygium excision and beta irradiation (Table 1). None were symptomatic. Four had recurrent pterygia present, to make a total of 12 eyes (16%) with recurrent pterygia after excision and beta irradiation. The conjunctiva was mildly abnormal in 6 fellow eyes (46%). Thirty-eight fellow eyes had no previous beta irradiation. Six eyes (16%) had untreated pterygia. One of 5 pterygia previously treated by simple excision alone had recurred.

CORNEAL ULCERATION

Indolent corneal ulcers occurred in 2 patients. One was aged 34 years at the time of initial unilateral pterygium treatment with simple excision and beta irradiation with 5000 rads in 3 doses over 2 weeks. An elliptical strontium applicator, active area of 13×18 mm and emission rate of 14.8 rads s^{-1} , was used. The eye was persistently sore and irritable after treatment until 10 years later, when a diagnosis of corneal ulceration was made (Fig. 6).

The ulceration of half corneal thickness was vertically oval and measured 2×3 mm. The edge was 1 mm from the limbus and situated at the site of the previous pterygium head. The ulcer edge and base were irregular, and the bulbar conjunctiva had a large avascular patch surrounded by prominent telangiectatic vessels. The tear film was normal and there was no corneal staining elsewhere.

The other patient who developed corneal ulceration was aged 36 years at the time of treatment 12 years before examination. Bilateral pterygia were excised and beta irradiation with 3600 rads in 3 doses over 2 weeks given.

A round, flat strontium-90 plaque of emission

rate 7.8 rads s^{-1} as well as the elliptical plaque mentioned above was used. The eye settled until 3 years prior to examination, when a sore left eye developed after irritation from sawdust. Nasally a 4×4 mm patch of bare sclera surrounded by a few telangiectatic vessels were present. Mild rose Bengal staining was found. A half-thickness oval corneal ulcer measuring 1.5×2.5 mm was situated at the site of the previous pterygium head and was separated from the limbus by 1 mm of almost normal cornea. The tear appearance was normal, but a Schirmer's test was 18 mm in the affected eye compared to 5 mm in the fellow normal eye.

SYMBLEPHARON AND PTOSIS

Three eyes (6%) with scleral ulceration had symblepharon. One patient treated with simple excision and 5200 rads over 3 weeks (12 years later) had marked symblepharon to the upper canalicular area and punctum. Another patient had simple excision 3 times to both eyes before excision and beta irradiation with 4800 rads over 4 weeks. Extensive symblepharon to both canalicular areas with punctal occlusion and tethering of the globe was present 16 years later. A third patient had recurrent bilateral pterygia treated by excision and beta irradiation with 3600 rads over 2 weeks. The right pterygium recurred within 3 months and was treated by excision and 2300 rads as a single dose. 3 mm of ptosis had persisted since treatment, and 11 years later symblepharon to the upper canalicular area was also present.

ASSESSMENT OF TEAR FUNCTION

A poor tear meniscus, decreased fluorescein break-up time, a Schirmer's test less than 5 mm in 5 minutes, and punctate corneal staining occurred alone or in combination in 17 patients (30%). Thirty-five patients (70%) had a normal tear assessment. In 14 patients (26%) the tear assessment was abnormal bilaterally despite the presence of an untreated fellow eye in 12 of these patients. Five patients were not examined. Ulcerated eyes had a Schirmer's range of 10 to 35 mm (mean 18 ± 10) in 5 minutes, while fellow eyes measured 2 to 35 mm (mean 14 ± 10). In none was tear production less and in 13 (25%) it was 6 mm more in ulcerated than in fellow eyes. Rose Bengal staining of the ulcer base was a constant feature. Adjacent bare sclera stained in 34 ulcerated eyes (63%).

Figs. 1-8 Late complications of pterygium treatment. (1) Superficial scleral ulceration with avascular conjunctiva, mild telangiectasia, and encrustation. (2) Moderately deep scleral ulceration inferiorly situated. (3) Deep scleral ulceration. (4) Inferiorly situated scleral ulceration with aphakia. (5) An atypical scleral ulcer with overlying conjunctiva. (6) Indolent corneal ulceration and a large area of bare sclera. (7) Sectorial posterior lens opacity, scleral ulceration, and an encrustation. (8) *Pseudomonas endophthalmitis* with hypopyon and ulceration within an area of bare sclera.

Table 6 Late complications of pterygium treatment: correlation of lens complications with patient details, treatment, and external pathology

Lens state	Visual acuity	Patients (no.)		Eyes (no.)				
		Age	Follow-up	Total dose	Ulceration	Treated fellows	Surface pathology	Untreated
Normal	6/9 or better	44 ± 10 (30)	10 ± 3.2	3101 ± 1004 (34)	27	8	8	32
Significant opacity	6/9 or better	48 ± 12 (13)	13 ± 2.9	4179 ± 730 (14)	14	3	2	3†
Cataract	6/18 or worse	62 ± 6.7 (7)	11 ± 1.2	3540 ± 858 (10)	4	1	0	0
Aphakic					6	1	0	2
Excluded*		12 patients		18 eyes	2	0	3	0

*Repeated and overlapping fields of irradiation (7) and unknown (5). †None sectorial.

IRIS PATHOLOGY

Localised nasal iris atrophy was present in both eyes of 1 patient 9 years after bilateral pterygium excision with 4500 rads over 3 consecutive days. The atrophy involved the 1 to 5 clock hours central to the collarette in one eye and a patch extending from the nasal pupillary margin to the iris root in the other eye. Another patient had 2 abnormal iris vessels on the nasal side in association with a scleral ulcer.

CATARACT FORMATION

Nine patients (16%) had 14 eyes with reduced vision from cataract (Table 4). Ten of these eyes also had scleral ulceration. This group represented 19% of all ulcerated eyes. In 2 of the 5 cataracts marked sectorial opacities extended from the nasal side and reduced vision. Patients with reduced vision or aphakia were significantly older at age of treatment ($P<0.001$) but had not been followed longer ($P<0.15$) than patients with normal vision. Total dose of beta irradiation was not significantly different from that given to eyes without cataract ($P<0.1$) (Table 6).

Sectorial cortical opacities with normal visual acuity were found in 19 treated eyes (25%) (Table 6). Minimal opacities limited to the equator or only faintly visible were excluded. Sixteen had a single course of beta irradiation with a total dose of 2900 to 5500 rads, while 3 eyes had additional beta irradiation (Table 2). The opacity was present mainly in the posterior cortex and in the same quadrant as the scleral ulceration (Fig. 7). The anterior cortex was involved in more severe cataracts. Thirteen eyes (25%) with scleral ulceration and 1 with corneal ulceration had such opacities. No equivalent opacities were seen in these eyes on the temporal side or in untreated fellow eyes. Three untreated eyes had diffuse equatorial or posterior polar cataracts. There was no significant difference in age ($P<0.15$) between patients with and without

sectorial opacities, but those with opacities had been followed up significantly longer ($P<0.01$). The total dose of beta irradiation was significantly greater ($P<0.001$) for eyes with sectorial opacities and normal vision than for those without opacities (Table 6).

PSEUDOMONAS ENDOPHTHALMITIS

This has occurred in 4 patients. All had deep scleral ulceration. Three have been reported elsewhere by the authors.⁵ The fourth developed endophthalmitis 3 months after inclusion in this survey. The patient, a 71-year-old female, had a pterygium excision and 4500 rads over 2 weeks 9 years before the sudden onset of ocular symptoms and the diagnosis of a scleral ulcer. Two years later, on inclusion in this survey, a 2×3 mm clearly defined deep scleral ulcer 2 mm from the limbus in the horizontal meridian was present associated with an encrustation and severe telangiectatic vessels. The tear film and Schirmer's test were normal. A nasal sectorial lens opacity was present. Three months later the eye spontaneously became red and painful. A large avascular area of sclera surrounded the ulceration. Peripheral corneal infiltration and a large hypopyon were present together with a mucopurulent discharge (Fig. 8). A moderate growth of *Pseudomonas aeruginosa* was cultured from the ulcer surface. Six days of treatment with gentamicin drops hourly and subconjunctival injection daily with oral amoxycillin was ineffective. This treatment was replaced by a continuous infusion of tobramycin into the upper fornix and intravenous ticarcillin as previously reported.⁵ An initial rapid reduction in the hypopyon was followed by a slow improvement. During the following 3 weeks she developed peripheral corneal vascularisation, mild iritis, posterior synechiae, and a dense cataract. Visual acuity was perception of light. Treatment was then continued with Chloromycin ointment (chloramphenicol and polymyxin B) 5 times a day for a further three

weeks. Two of the eyes with *Pseudomonas aeruginosa* infection were eviscerated and 2 salvaged after 6 to 7 weeks' hospitalisation. One retained normal visual acuity and the other suffered profound visual loss due to complicated cataract.

RELATIONSHIP OF RADIOTHERAPY TO SCLERAL ULCERATION

Bilateral deep scleral ulceration occurred in 5 patients after identical treatment to each eye. Each eye had a single pterygium excision and beta irradiation with 2400 to 4400 rads (mean 3460 ± 780).

Unilateral ulceration occurred in the presence of an untreated fellow eye in 29 patients. Five were superficial, 7 moderately deep, and 18 deep ulcers. Three eyes had had repeated courses or overlapping fields of beta irradiation (Table 2). Apart from these 3 irradiation dosage ranged from 750 to 5200 rads (mean 3386 ± 1079). The remaining 12 patients had unilateral scleral ulceration despite bilateral pterygium treatment. Nine patients had similar treatment given to each eye. Eight had a single course of beta irradiation (range 2400 to 4800 rads, mean 3437 ± 944). One ulcer was superficial, 1 moderately deep, and 6 deep. One patient had bilateral repeated beta irradiation with unilateral atypical ulceration (Table 2, no. 5). Three patients developed ulceration only in the eye given additional beta irradiation (Table 2). Apart from retreated and overlapping fields of beta irradiation 1 eye had a single dose of 750 rads and the remainder had fractionated treatment (Table 3) with a total dose of 2000 to 2400 rads in 10 eyes, 2500 to 3400 in 9 eyes, 3500 to 4400 in 25 eyes, and 4500 to 5200 in 7 eyes. Six patients with ulceration were initially treated before 1964, 12 during 1964–6, 22 during 1967–9, 5 during 1970–2, and 1 in 1974.

Discussion

Cosmesis, irritation, or threatened vision are standard indications for pterygium treatment, yet most do not cause marked discomfort or limit vision.^{1,6} Reduced visual acuity from untreated pterygia was present in only 0.2% of 1352 patients⁷ in one series and other reports are of single cases.^{1,8} The efficacy of pterygium treatment is limited by a high recurrence rate without beta irradiation^{1,7} and other complications. Apart from recurrence rates, late complications have received little attention.

Patient acceptance of treatment and subsequent ocular discomfort should be important considerations in pterygium treatment. Treatment was a painful experience in 32% of the population we studied, and this was universally attributed to beta irradiation. Pain may arise from repeated mechanical damage during application or from acute punctate

corneal erosion.⁹ Ocular discomfort and photophobia persisted for many years in 42% of our subjects despite protective measures and topical treatment. The severity of symptoms did not correlate with the size or depth of scleral ulceration.

Scleral ulceration after pterygium excision and beta irradiation has been previously reported.^{10–15} In our 46 patients with 52 scleral ulcers the depth of ulceration did not correlate with patient age at treatment, follow-up time, or total dose of radiation. The ulcer was inferiorly situated in 7 eyes (13%). This would be consistent with elevation of the eye during radiation treatment if ulceration occurs at the point of contact of the applicator on the eye. The nature and timing of ulceration, the appearance of the sclera and adjacent tissues, and the development of ulceration only after additional beta irradiation clearly implicate radiation induced pathology in the pathogenesis of scleral ulceration. However, sclera is generally known to be radioresistant. Very high doses of beta irradiation to rabbit eyes have produced no scleral ulceration.¹⁶

In man beta irradiation to the posterior sclera with up to 100 000 rads over 8–14 days did not cause necrosis in 62 patients followed up for 1 to 9 years (mean 4 years).¹⁷ Reports of 'partial scleral sloughing'¹⁸ and scleral necrosis^{19,20} following very high doses of cobalt-60 plaque treatment do exist but are rare. At least 1 such case occurred anteriorly in association with the conjunctiva.¹⁹ On the other hand high doses of radiation are not necessary for scleral ulceration to develop anteriorly.¹⁵ Even with the currently used dose of 2400 rads or less, 11 scleral ulcers were seen in our series. It would appear that an additional factor contributes to 'radionecrosis' of the sclera anteriorly. Possible factors include surgical damage, scleral exposure, the influence of damaged conjunctiva, or the tears.

Faulty surgical technique, particularly cautery, has been implicated.^{6,10,12} An irregular distribution of translucent spots within the bare sclera followed the use of a heavy tipped cautery in 1 reported case.¹² In our survey 3 eyes had translucent spots, but in an area equidistant from the limbus. A small vascular tuft arose from some spots. The appearance suggested that these spots developed at the penetration site of anterior ciliary vessels. The location would be more random if due to surgical damage. The appearance of 1 atypical case (Table 2, no. 5) did suggest a scleral incision.

The possible role of exposure has been the subject of a short-term experimental study in rabbits by the authors (to be published). It has been found that exposure alone may cause rapid and indolent scleral necrosis. Bare sclera persisting after pterygium treatment has been previously noted and may

occur without symptoms in many patients.^{1 10 12 13} Four of our patients (61%) were noted to have persistent bare sclera for 1 to 7 years before developing ulceration. In eyes that do regain conjunctival cover late conjunctival necrosis could precede scleral ulceration. The presence of bare sclera in almost all ulcerated eyes and the occurrence of ulceration after low doses of radiation suggests that conjunctival breakdown is the first event.

In this survey ulcerated eyes had a slightly greater tear production than nonulcerated fellow eyes ($P < 0.05$). Therefore it is felt that lack of tears is not a significant factor.

Pseudomonas endophthalmitis occurred in 4 patients with deep scleral ulceration. Three have been reported by the authors.⁵ A spontaneous onset occurred in 3, and the relationship to scleral ulceration was undeniable. Two eyes came to evisceration and 2 were salvaged only after intensive and prolonged hospital treatment. The occurrence of endophthalmitis emphasises the importance of surgical repair of radiation induced deep scleral ulceration.

Corneal ulceration has been reported⁹ after pterygium excision and very high doses of radium-D beta irradiation or in widespread corneal disease or from external beam irradiation. Two cases of corneal ulceration are described here. Both were indolent with necrotic margins and no inflammation or vascularisation. They occurred at the site of the previous pterygium head. Corneal erosions may persist for up to 1 year after beta irradiation, and 1 case of corneal dystrophy has been described previously.²¹

Less important complications of treatment were also seen. A thinned vascular area of conjunctiva surrounded by telangiectatic vessels was commonly seen. It was not more severe in eyes with scleral ulceration. Symblepharon was present in 3 patients associated with a tethered globe in one and ptosis in another. This is a recognised complication of pterygium excision but can also occur after radiation treatment.¹⁹ Localised iris atrophy occurred bilaterally in one patient who also had lens opacities but normal visual acuity.

Beta irradiation-induced cataract is well documented. In one series 38 of 115 patients had non-progressive lens opacities when examined a minimum of 8 years after beta irradiation.²² 20% of patients who received less than 3600 reps developed opacities (1 rep=1.08 rads tissue). Hilgers²³ found no lens opacities 5 years after a fractionated dose of 3000 reps of strontium-90 beta irradiation, but 3 of 46 eyes (6%) developed lens opacities after 3000-5000 reps. This incidence was considered acceptable to maintain a low rate of pterygium recurrence. In

addition a single dose of 2200 rads after pterygium excision has been considered safe even when repeated twice for subsequent recurrences.¹ Typical sectorial posterior cortical lens opacities, with a visual acuity of 6/9 or better, were present in 19 eyes (25%) in this survey. The total dose of beta irradiation ranged from 2900 to 5200 rads (Table 6). The anterior cortex was involved only in the more severe cataracts, an observation previously noted.²⁴ Compared to patients without cataract our patients showed no significant difference in age or length of follow-up, but a strong correlation was found with respect to the total dose of radiation ($P < 0.001$). This survey confirms that some opacities will develop after a fractionated dose of 3000-5000 rads.

Reduced vision from beta irradiation-induced cataract is not common. Seven cases occurred 3 to 6.5 years after radium beta irradiation.²⁵ None has been reported after pterygium excision and strontium-90 beta irradiation. In this study radiation-induced cataract caused reduced vision in 3 patients. (Table 4, nos. 1, 2, 3). The influence of beta irradiation on cataract formation in the other 6 patients in Table 4 cannot be determined. The fact that these patients were older at treatment than those with normal vision ($P < 0.001$) probably reflects the distribution of senile cataract rather than any susceptibility of the older lens to radiation. It is the younger growing lens that is particularly susceptible.

This survey would support a more cautious attitude both to the management of pterygium and to the use of beta irradiation. The complications of treatment, especially scleral necrosis and cataract, may lead to visual loss. With scleral ulceration, surgical treatment may be indicated to relieve symptoms alone and should certainly be considered for deep scleral ulceration to prevent *pseudomonas* endophthalmitis. The development of cataract after treatment of a benign lesion is not acceptable. There is a need to reconsider the indications for surgical treatment and the application of beta irradiation. Lower doses of radiation may reduce the complication rate but may also be less effective in preventing recurrence.

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Preinvasive carcinoma of the cornea and conjunctiva

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SUMMARY Greyish-white spots, varying in size, caused diagnostic problems in 2 patients with pre-invasive corneal carcinoma. Keratectomy specimens permitting light and electron microscopy indicated that the smaller spots predominating in one patient correlated with epithelial microcysts and vacuoles, while areas of parakeratosis accounted for the macroscopic white patches found in the other. A variety of ultrastructural abnormalities, including excessive basement membrane fibrillogenesis, were present in both cases.

When carcinoma-in-situ involves the cornea it usually appears as a greyish (rarely pigmented) gelatinous elevation extending from the limbus on to the cornea. In contrast the 2 patients reported here presented with a translucent film-like change of the central epithelium in which white dots, microscopic in the first patient but visible to the naked eye in the second, were present. These somewhat unusual clinical findings, together with correlated light and electron microscopic appearances, have prompted this report.

Case reports

CASE 1

A 29-year-old white male was first seen in May 1971, at age 22, complaining of blurred vision in his left eye, which was irritable and watered, especially when reading. His right eye was normal apart from a refractive amblyopia and a small biopsy-confirmed squamous papilloma of the outer canthus. Visual acuity of the left eye corrected to 20/40, though several weeks previously it had been 20/15. The patient's general health in adult life had been unremarkable except for a gonococcal urethritis a year ago; this had responded rapidly to penicillin. Biomicroscopically the left cornea showed 'subepithelial dot-like infiltrates and diffuse clouding of the superficial stroma while a superficial pannus extended inward 2 mm from the limbus'. There was no vital staining of the cornea. Keratitis of unknown

cause, possibly viral, was suspected. Topical treatment with tetracycline and hydrocortisone eye ointment produced no improvement. The patient refused biopsy.

Over the intervening years symptoms of irritation subsided, but there was a gradual deterioration in vision of the left eye, which by October 1977 was 20/100, not improved with spectacles or contact lenses. Biomicroscopy of the affected cornea at this stage revealed a greyish ground-glass appearance of the epithelium and superficial stroma. The corneal epithelium and adjacent conjunctiva were studded with myriads of white dots of various diameter which were just visible at $\times 20$ magnification (Fig. 1A). Corneal sensation was normal and there was no vital staining.

An 8 mm perforating graft of the affected left cornea was undertaken. Histological examination of the host disc showed severe dysplasia of the corneal epithelium alternating with areas of carcinoma-in-situ. This diagnosis stimulated further examination of the left eye, when it was observed that there was widespread thickening of the bulbar conjunctiva terminating abruptly some 5-8 mm from the limbus. In the affected conjunctiva a fine papillary or vertical 'corkscrew' type of neovascularisation was rendered more obvious by the general postoperative congestion (Fig. 1B). Multiple biopsies confirmed the extent of conjunctival involvement delineated with the slit-lamp.

After several weeks the corneal graft became covered with epithelium which resembled the host tissue in that it was translucent and contained many small white dots. An attempt to remove the affected epithelium was made. The corneal epithelium was

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Fig. 1 Case 1. A. Corneoscleral junction. Microcysts appear as myriads of white dots (arrows) in carcinomatous epithelium. Black dots at upper left are vertical new vessels seen end on. Inset shows microcysts in thickened corneal epithelium. B. Detail of conjunctival new vessels which have a frond-like configuration.

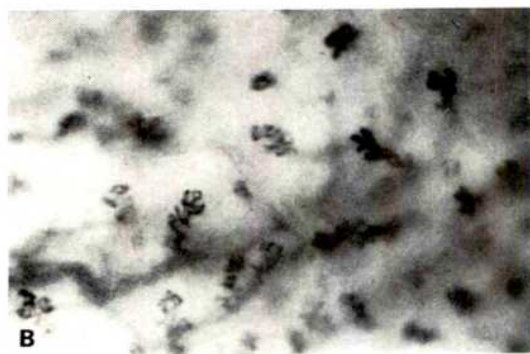


Fig. 2 Case 2. White plaque-like and smaller dot opacities superficially in a translucent, avascular, preinvasive carcinoma of the cornea.

dried and then liberally painted with absolute alcohol, followed by debridement. The diseased conjunctiva with a few millimetres of apparently healthy tissue was excised, but probable residual tumour was shown in 3 quadrants microscopically. Three weeks later the denuded area was covered by regenerated epithelium which was translucent, thickened, and again contained white dots. Biopsy indicated recurrence of the dysplasia/carcinoma-in-situ. Observation over the past 2 years has shown no clinical change.

CASE 2

A 52-year-old white male in excellent general health was first seen by us in January 1970. He stated that a greyish lesion of the right cornea had been present for the past 2 years. The condition had begun with severe irritation and blurred vision initially diagnosed as a viral keratitis. After the initial acute episode the greyish central corneal lesion had not

changed much until recently, when it became noticeably raised. His ophthalmologist had noticed that the lesion contained white dots of varying size, some of which were visible to the naked eye. These he had considered as calcific plaques and had removed them from time to time. Over the past 3 months the lesion had become raised and extended toward the inferotemporal limbus (Fig. 2). Biopsy revealed a well differentiated squamous carcinoma-in-situ of the corneal epithelium. Excision of the tumour by lamellar keratectomy together with removal of the adjacent limbal conjunctiva and Tenon's capsule was undertaken. The tumour did not recur. The patient died from coronary thrombosis 3 years later.

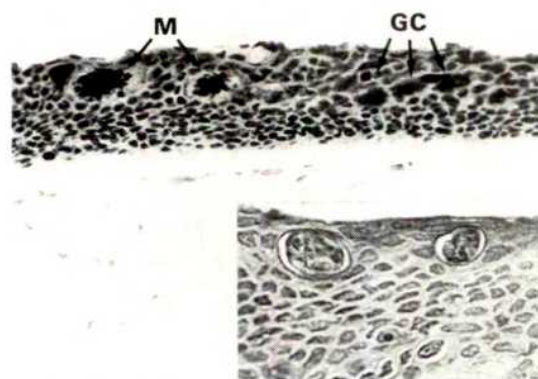


Fig. 3 Case 1. Carcinoma-in-situ of the corneal epithelium showing 3 large epithelial giant cells (GC), and two microcysts (M) containing dense basophilic material. (H & E, $\times 175$). Inset: Microcysts are lined by Alcian-blue-positive material like that of the superficial squames. ($\times 295$).

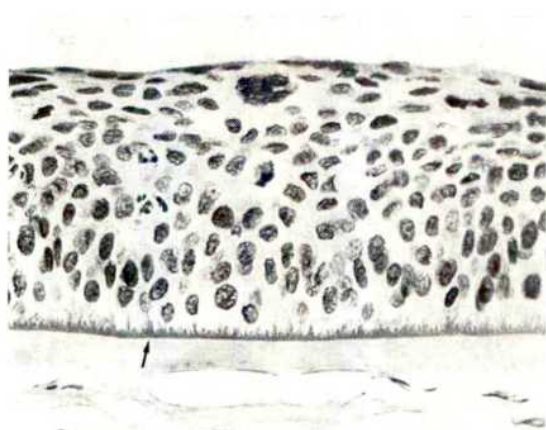


Fig. 4 Case 1. Fern-like extensions of the basement membrane (arrow) between the basal corneal epithelial cells. An epithelial giant cell is present near the surface centrally. (PAS, $\times 433$).



Fig. 5 Case 1. Bulbar conjunctiva showing abrupt junction of carcinoma-in-situ with normal conjunctiva. (H & E, $\times 96$).

Methods and materials

The 2 keratoplasty specimens were fixed in 10% neutral buffered formalin and divided. Half of each was embedded in paraffin for light microscopy and routine histochemistry. The other halves were osmified, embedded, and sectioned in epoxy resin prior to transmission electron microscopy. Conjunctival biopsies from case 1 were treated similarly.

Results

LIGHT MICROSCOPY

Case 1. The corneal disc showed abnormalities which were confined to the epithelium and superficial stroma. The epithelium was hyperplastic, the

normal 5 layers being increased to 12 or more. Areas of dysplasia in which loss of basal polarity was a prominent feature alternated with areas of carcinoma-in-situ showing hyperchromatism, epithelial giant cells, pleomorphism, and abnormal mitoses (Fig. 3). Numerous microcysts were present in all areas of the epithelium. Several types were evident. Cysts of 40–100 μm contained debris which stained with Alcian blue, colloidal iron, and periodic acid Schiff (PAS). Smaller cysts contained a single shrunken densely stained cell. Finally, there were small cystic spaces which appeared almost empty apart from fine granular aggregates. In most sections vertical tufts of basement-membrane-like



Fig. 6 Case 2. Carcinoma-in-situ of corneal epithelium showing large epithelial whorls and patch of parakeratosis (P). There is pannus under the epithelium, but the basement membrane is intact. (H & E, $\times 124$).

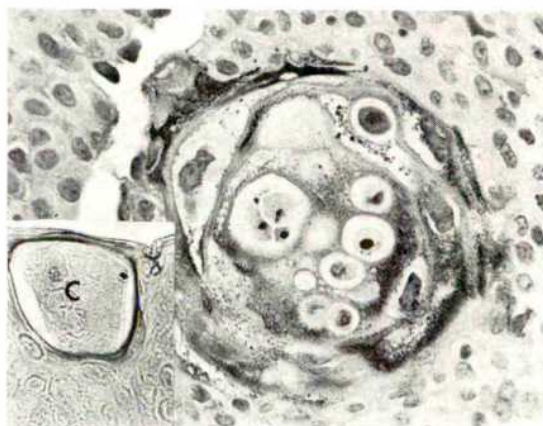


Fig. 7 Case 2. Corneal epithelium showing large dyskeratotic whorl containing many microcysts. (H & E, $\times 337$). Inset: Wall of microcyst (C) staining with Alcian blue. ($\times 293$).

material extended into the basal cell layer (Fig. 4). There was no evidence of extension of the epithelial cells through the basement membrane. No subepithelial inflammatory cells were present, but there was minimal anterior stromal scarring.

The conjunctival biopsies showed similar changes, but in addition capillaries with a minimum of con-

nective tissue extended from the lamina propria into the epithelium in the limbal area. The transition to normal conjunctiva at the edges of the lesion was characteristically abrupt (Fig. 5) with a tendency for the carcinoma to override the normal epithelium.

Case 2. The corneal epithelium showed changes

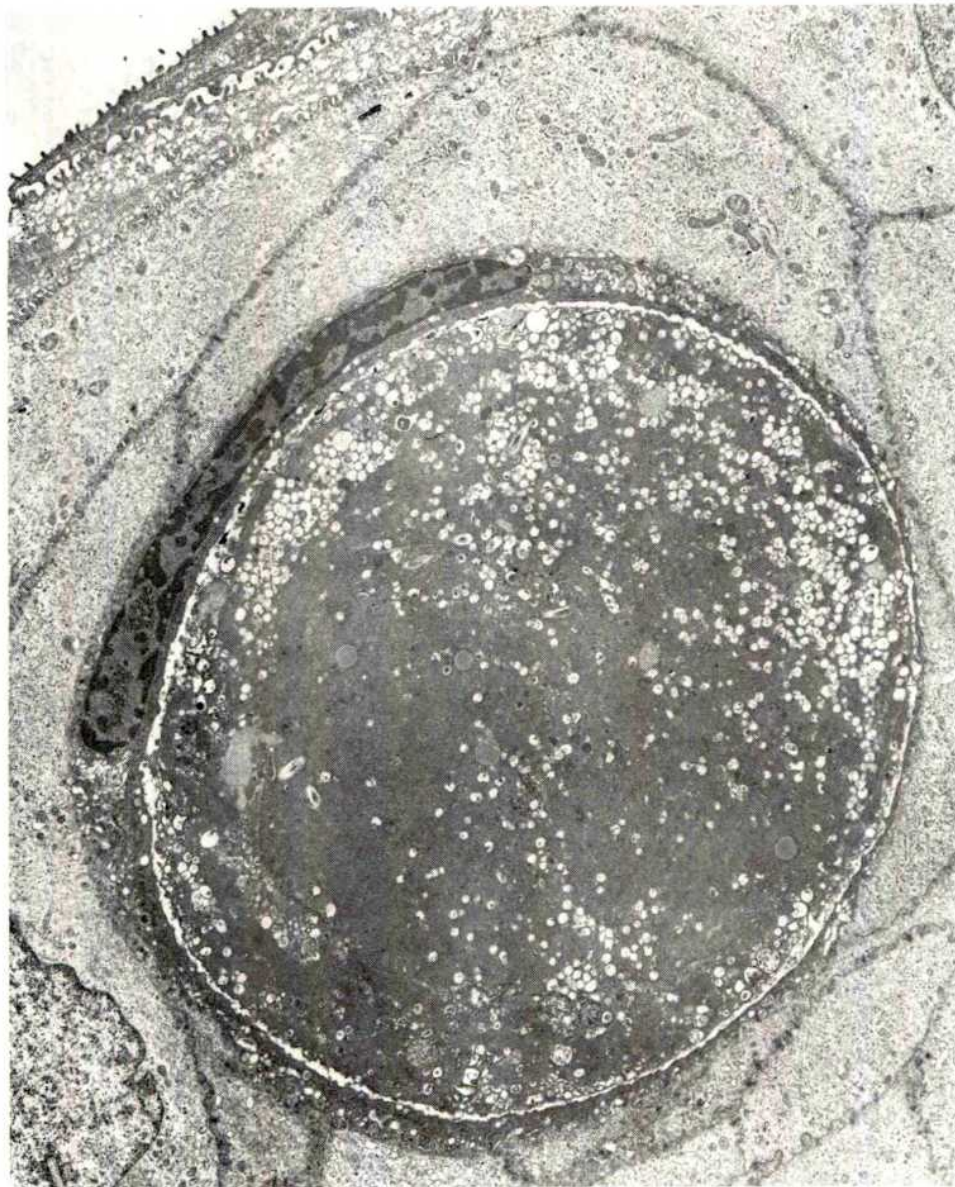


Fig. 8 *Case 1.* Large microcyst. Lining shows few microvilli. Cyst contents include vacuolated electron-dense material and other cell debris. Adjacent cells contain some increase in mitochondria, endoplasmic reticulum, and tonofibrils for this layer. (TEM, $\times 6160$).

of keratinising carcinoma-in-situ. The grossly disordered epithelium showed numerous mitoses as well as occasional giant cells, dyskeratotic whorls of cells, and parakeratosis (Fig. 6). Nests of dyskeratotic cells, some of which were encysted (Fig. 7), were regularly seen. Small microcysts similar to those in case 1 were present (Fig. 7, inset) but not frequent. Bowman's layer, although absent in places, was not invaded by tumour, and the basement membrane appeared intact. In some areas a layer of loose fibrillar material often showing a striated appearance was interposed between Bowman's layer and the basement membrane (Fig. 13, inset A). This material stained poorly with PAS but was strongly coloured with Alcian blue. The stroma underlying the tumour was moderately vascularised and infiltrated with lymphocytes and occasional plasma cells. Capillaries from this layer extended vertically into the tumour.

ELECTRON MICROSCOPY

The cancerous epithelium in both cases contained an excessive number of organelles, including mitochondria, endoplasmic reticulum, and tonofilaments (Fig. 8). There appeared to be a reduction in desmosomes, which in places had become invaginated or engulfed and lay free within the epithelial cell cytoplasm (Fig. 9).

Microcysts containing disintegrating cytoplasmic debris and organelles were particularly frequent in case 1 (Fig. 8). The cyst walls were formed by the cell membranes of adjacent cells which had become flattened and wrapped around the contents. The

lining membrane thus formed was often wavy in outline but rarely showed well formed microvilli. Occasionally disintegrating cells had been engulfed by epithelial phagocytes without a surrounding cell membrane (Fig. 10). In case 1 the neoplastic epithe-

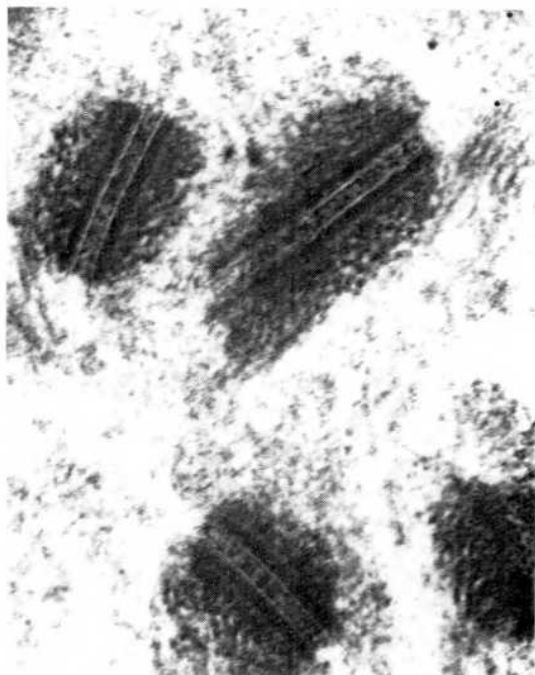


Fig. 9 Case 1. Cluster of desmosomes lying free within cytoplasm of corneal epithelial cell. (TEM, $\times 20\ 816$).

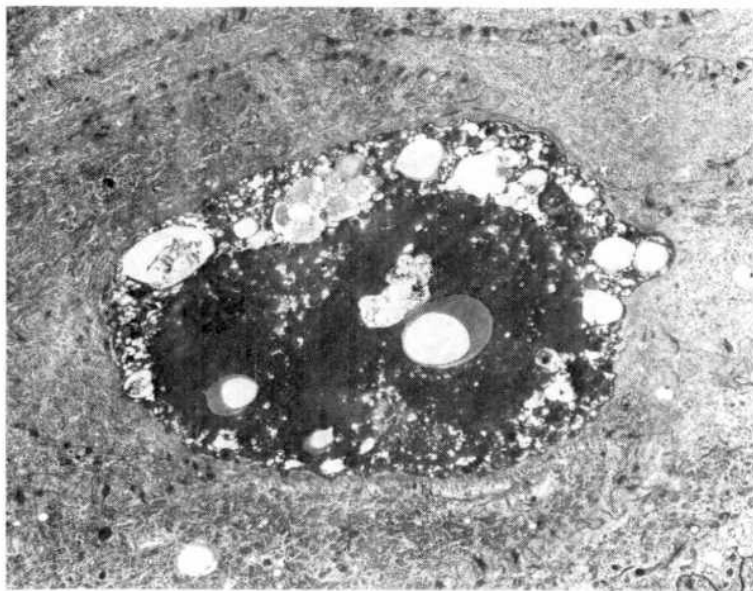


Fig. 10 Case 1. Corneal epithelial cell has engulfed a disintegrating cell. (TEM, $\times 4955$).

lial cells of the middle layer often contained large cytoplasmic vacuoles in which dense amorphous material intermixed with fibrils 14–16 nm wide with microbanding at 3 nm were found (Fig. 11). In some of these vacuoles the amorphous material

was arranged in circumferential bands with the fibrils lying in groups of 2–6 parallel to each other and perpendicular to the amorphous material; in others both elements were unoriented.

Basement membrane alterations were prominent

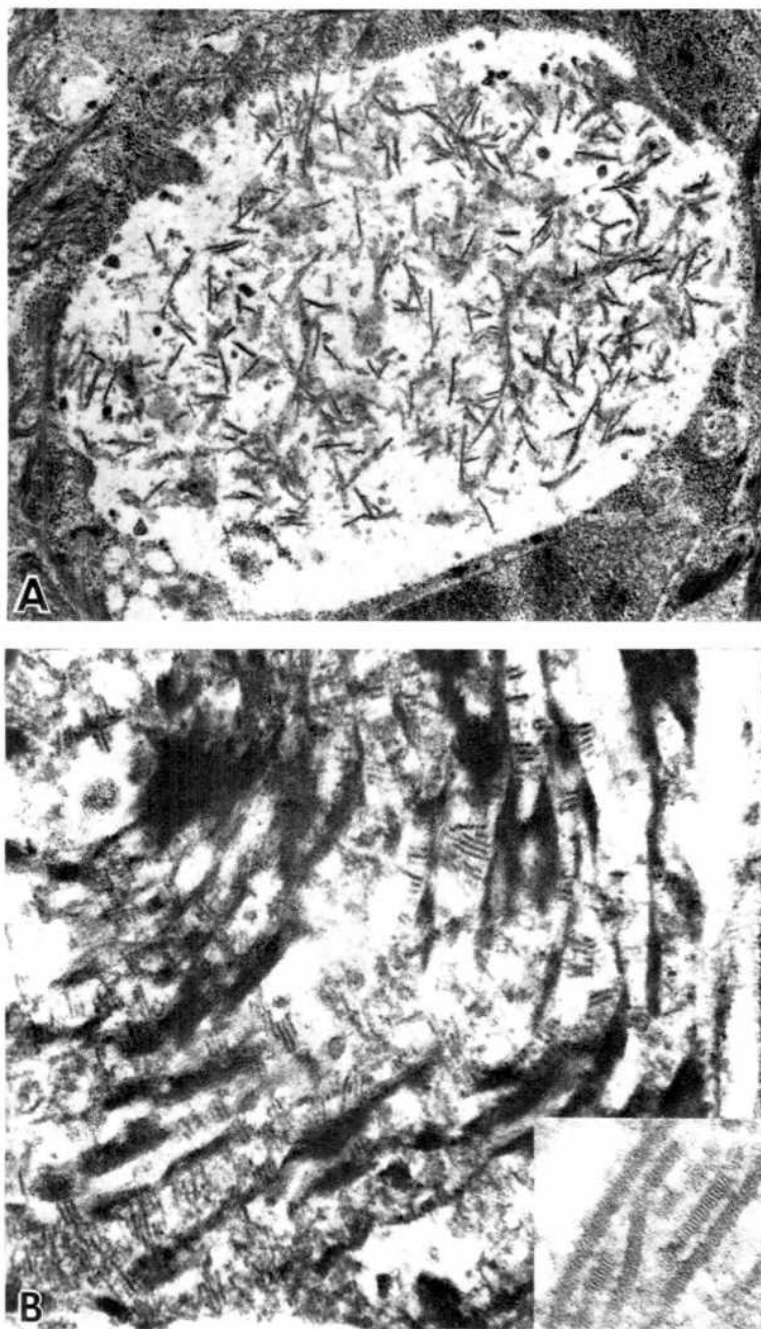


Fig. 11 Case 1. Corneal epithelium. Intracytoplasmic vacuoles containing amorphous material mixed with fibrils. In A these 2 elements are arranged randomly. (TEM, $\times 24\,000$). In B the fibrils are parallel to each other and lie perpendicular to the amorphous material, which is disposed circumferentially. (TEM, $\times 37\,612$). Inset B: The fibrils are banded at 3 nm. (TEM, $\times 177\,672$).

in both patients. In case 1 a layer of amorphous granular material was found between the basement membrane and Bowman's layer. At regular intervals the basement membrane was thrown into vertical frond-like folds (Fig. 12) corresponding to those

seen by light microscopy (Fig. 4). Besides granulomatous material, the core of these protrusions contained collagen-like fibres with coarse banding at 55 nm and a microperiodicity of 9 nm. In case 2 similar fibrillogranular material sometimes con-

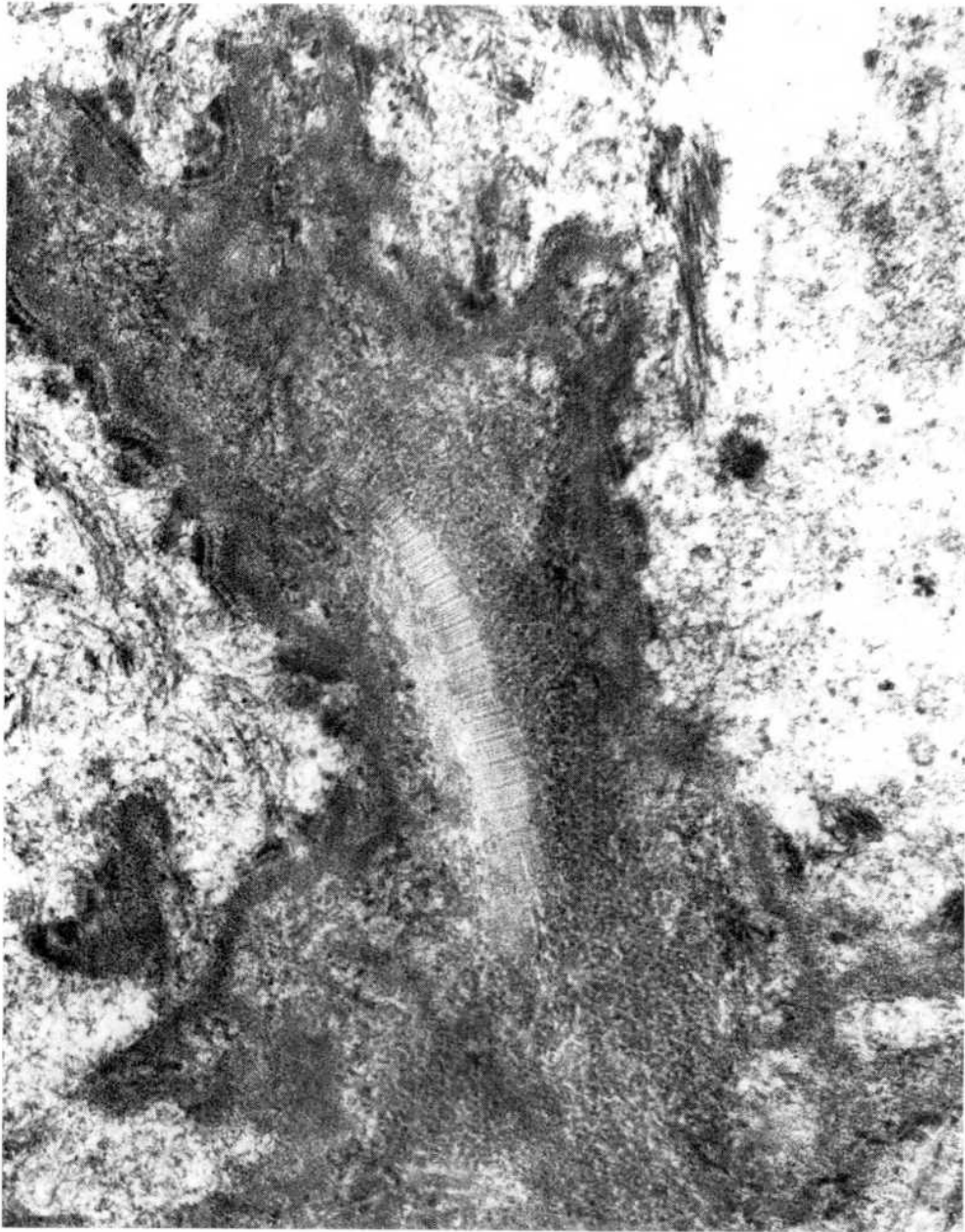


Fig. 12 Case 1. Corneal basement membrane is thrown into vertical folds by accumulation of abnormal fibrillogranular material beneath it. Folds often contain prominent fibrils banded at 55 nm as here. (TEM, $\times 59\,210$.)

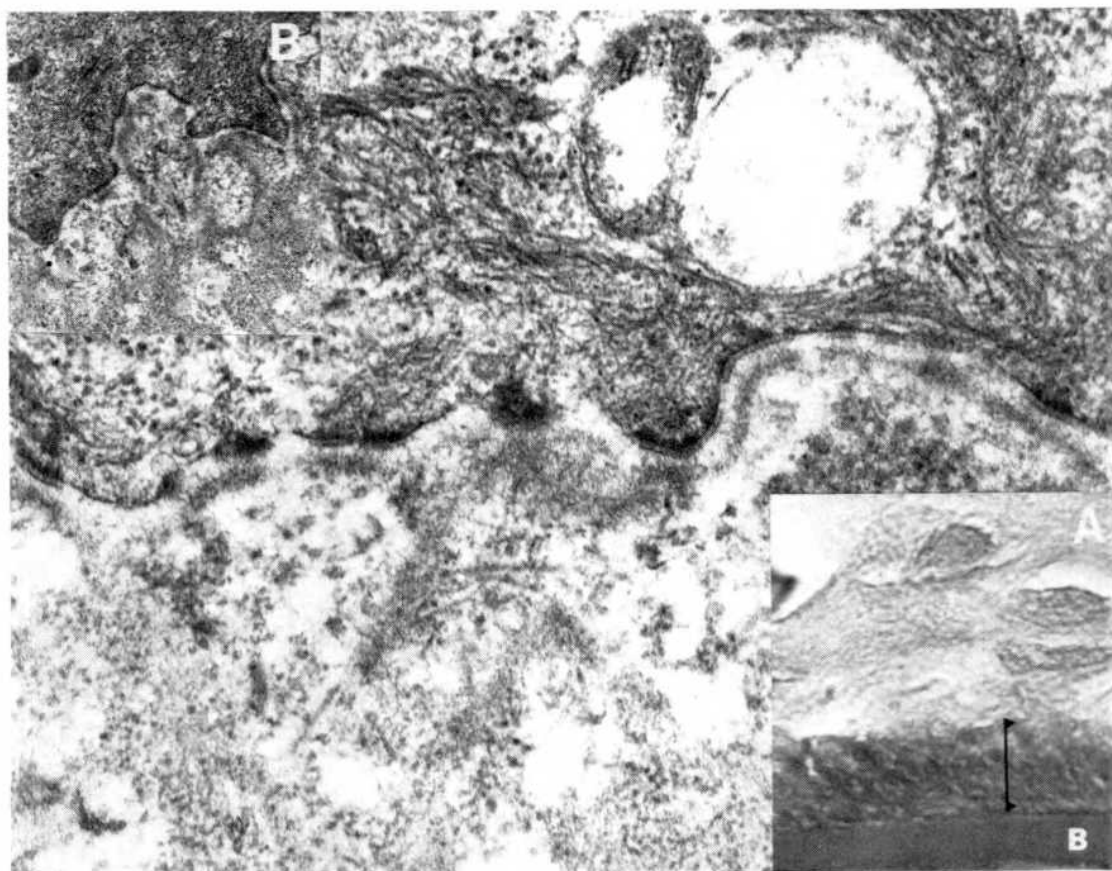


Fig. 13 Case 2. Corneal epithelial basement membrane rests on a fibrillogranular layer of abnormal material. (TEM, $\times 51\,280$). Inset A: By light microscopy this layer (bracket) has an oblique striated appearance. B = Bowman's membrane. (H & E, $\times 977$). Inset B: Processes of the basal cells extend irregularly into this thick layer. (TEM, $\times 17\,337$).

taining dense bodies and vacuoles was interposed between the basement membrane of the irregular basal epithelium and Bowman's layer (Fig. 13).

Discussion

This report concerns 2 cases of carcinoma-in-situ of the cornea and in 1 case also of the bulbar conjunctiva. There was neither clinical nor microscopic evidence of inflammation at the time we studied them, although an acute superficial keratitis had given rise to the initial symptomatology in both patients. The biomicroscopic appearances, somewhat vaguely recorded, had suggested a viral aetiology to their ophthalmologists. Such inflammatory episodes occurring as a prelude or accompaniment of carcinoma of the conjunctiva have been often noted in the past. Thus Irvine¹ reported 3 cases of diffuse

growth involving the bulbar conjunctiva (not unlike our first patient) in whom marked inflammation obscured their carcinomatous nature until conjunctival smears and biopsies were examined. It is of interest that 1 of these patients later developed regional metastases.

White dots were present in the lesions seen in both our cases. In the first patient they were visible biomicroscopically as myriads of white, epithelial punctae which did not stain with vital dyes. Microscopically they consist of microcysts and vacuoles of various sizes, scattered throughout the corneal and bulbar conjunctival epithelia. They appear to originate from disintegrating cells which have been subsequently enveloped by adjacent cells without actually being phagocytosed. In this respect they resemble epithelial microcysts seen in a variety of unrelated disorders which have been described by

Tripathi and Bron.² The plasmalemmal lining of the microcysts seen in our patient, however, was smooth or only slightly crenated in contrast to the prominent microvillous configuration seen in the microcysts found in other conditions. This difference may relate to the tendency for normal cell interdigitations to be lacking or absent in this type of carcinoma as noted by Tripathi,³ although it was not observed in our patients.

Intracytoplasmic vacuoles containing amorphous electron-dense material together with peculiar fibrils showing banding at 3 nm were regularly seen in the midepithelial layers of the first patient. Their origin is not known. Possibly they result from degradation and repolymerisation of fibrous proteins such as compose the tonofibrillar system, which was excessively developed in many cells. Vacuoles of this type were not observed in the second case, though there were occasional microcysts of degenerating cells. It may be deduced that the macroscopic white plaques seen in the second patient probably represented the extensive patches of parakeratosis observed microscopically. The presence of clusters of desmosomes dissociated from their parent cell membranes and lying free in the cytoplasm of epithelial cells was an occasional finding in both patients. This phenomenon was noted in Bowen's disease of the skin by Seiji and Mizuno⁴ as well as in preinvasive carcinoma of the cornea by Tripathi and Garner.³

Prominent ultrastructural changes which do not appear to have been previously noted in this condition were present in relation to the basement membrane of the corneal epithelium. In both cases a layer of fibrillogranular material was deposited between the basement membrane and Bowman's layer. In the first patient this substance covered by the basement membrane extended upwards as frond-like protrusions into the epithelium. A similar layer was seen in the second patient, but

interepithelial projections were not observed. It is probable that this basement-membrane-like material originates from the disordered epithelium. Microcysts of different types, together with abnormal basement membrane material, seem to represent the response of the corneal epithelium to a variety of unrelated stimuli.⁵

The junction between apparently normal epithelium and the thicker dysplastic or carcinomatous tissue was abrupt in both patients. This well recognised finding provides a means by which the limits of the tumour may often be determined in optical section of the slit-lamp. However, the diseased epithelium is sometimes only minimally thickened,⁶ so that the precise limits of bulbar extension must always be determined histologically by multiple punch biopsies. Cicatricial distortion of the conjunctival vessels at the healed biopsy sites permits their ready identification prior to definitive surgery or radiotherapy, or, when it is indicated, to further biopsies from more peripheral sites.

Miss Sharon Edwards was responsible for the technical aspects of microscopy in this report.

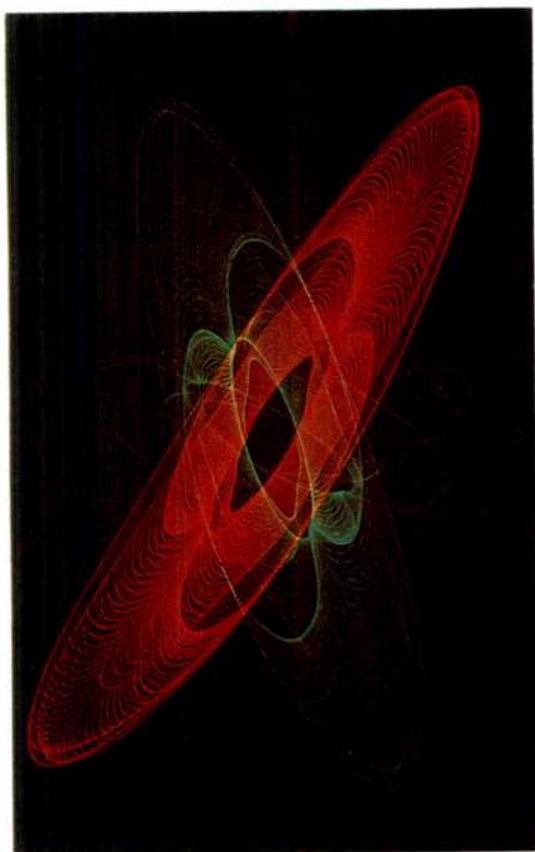
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Congenital fistulae of the lacrimal gland

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SUMMARY A 36-year-old man had congenital fistulae of the palpebral lobes of the lacrimal glands, with orifices bilaterally in the intermarginal strip of his upper eyelids near the external canthi. The left fistula was cystic and had become chronically inflamed. Because antibiotic therapy was unsuccessful, excision was necessary. Congenital fistulae are extremely rare, forming a lateral and tarsal group, each group having typical characteristics.

Congenital fistulae of the lacrimal gland are rare. We could find only 13 reports in the literature, usually affecting children. None of these descriptions reports a bilateral occurrence.

Case report

A 36-year-old man complained for a year of discharge of purulent material from the external canthus of his left eye, especially when he exerted pressure on the temporal part of his upper eyelid. Local therapy with antibiotics had failed. He had

no other complaints and was in a good health. Both eyes were normal.

In the intermarginal strip of both upper eyelids, just against the external canthus, a fistula could be seen with an orifice the size of a pin head. The conjunctiva of the left eye was hyperaemic, and a small yellow purulent discharge came from the fistula. The right eye was symptomless and normal lacrimal fluid exuded from the fistula. Apart from these 2 small openings the eyelids of both eyes were quite normal.

The purulent material from the left fistula proved to be sterile. With a probe 0.5 mm diameter the left fistula was traceable for 18 mm (Fig. 1) and the right for 4 mm. The lacrimal passages on both sides were normal.

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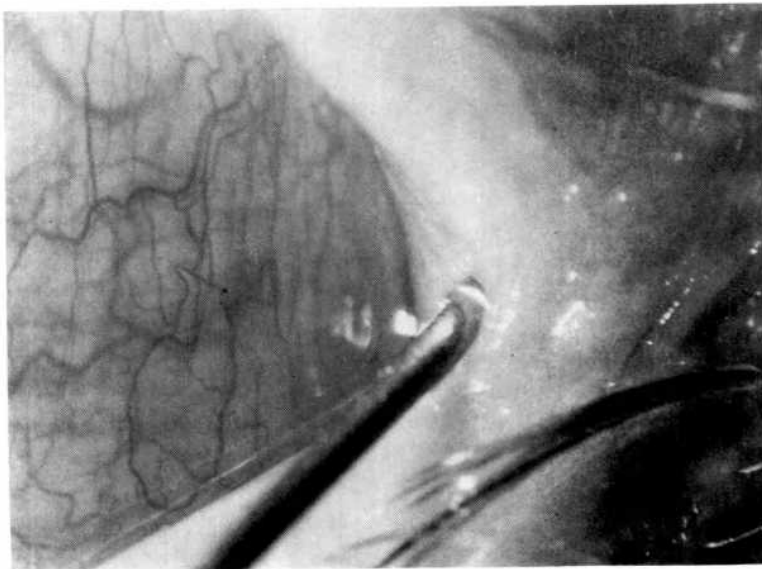


Fig. 1 Probe in the lacrimal gland fistula of the left eye.

Fig. 2 X-ray contrast photography demonstrating the cystic enlargement of the left fistula and the 2 diverticulae of the right fistula.

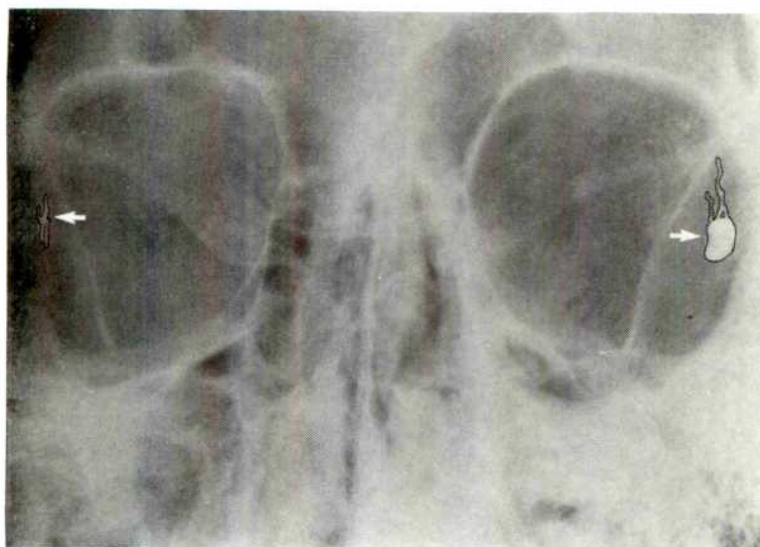
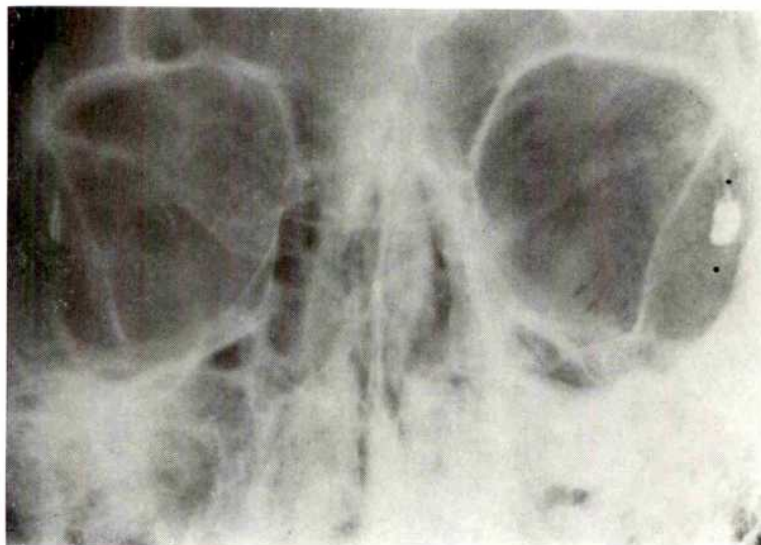


Fig. 3 The same photograph as Fig. 2 but with both fistulae outlined.

X-ray contrast photography showed the fistula on the left to be cystic just above the cutaneous orifice (Figs. 2 and 3). Cranially to this cyst 2 small ducts ran up in the direction of the palpebral part of the lacrimal gland. On the right side the fistula was straight and had 2 diverticulae.

As conservative therapy had failed, we decided to operate on the left fistula. Under general anaesthesia a probe 0.5 mm in diameter was pushed up to the palpebral part of the lacrimal gland. After turning the upper eyelid this probe was well seen just beneath the conjunctiva. With the probe as guide the conjunctiva was incised and the fistula was

totally extirpated together with some neighbouring tissue of the palpebral part of the lacrimal gland. The conjunctiva was then closed with 8-0 virgin silk.

The postoperative course was uneventful. After a follow-up of 1 year no recurrences or cysts were present in the operative field and the patient was symptom free.

On microscopic examination the wall of the fistula appeared to be composed of multilayered nonkeratinising squamous epithelium surrounded by connective tissue, with some polymorph nucleated inflammatory infiltrates.

Discussion

Lacrimal fistulae can be divided into 2 groups according to the situation and the anatomy of their orifice in the eyelid (Fig. 4).

(1) The tarsal group has the orifice near the upper rim of the tarsal plate of the upper eyelid, either in the centre or near the temporal canthus. In all the cases described a tuft of hair was found around the orifice.¹⁻⁴

(2) The lateral group has the orifice at some distance (3 to 35 mm) from the external canthus. A tuft of hair is never found around the orifice.⁶⁻¹³ With the exception of 1 case⁶ the eyelids have a normal anatomy.

Both fistulae of our patient were in the lateral group. The x-ray examination confirmed that both

tions. In contrast Ling,⁶ Schornstein,⁴ and Frey⁷ excised the fistulae together with the adherent piece of the lacrimal gland. This method was followed by us. The excretory ducts of the orbital part of the lacrimal gland run through the palpebral part before they end in the conjunctival fornix. Thus with the excision of a congenital lacrimal fistula one should take away only that part of the palpebral lobe of the lacrimal gland that drains into this fistula and certainly not more.

The epithelial lining of the excised fistula has been described in 3 cases. Ling⁶ and Schornstein⁴ found stratified squamous epithelium, but Terlinck² compared the wall of the fistula with cutaneous tissue and even described hair follicles and sweat glands. In our case we met with multilayered non-keratinising squamous epithelium with a chronically inflamed infiltrate underneath. The piece of palpebral lacrimal gland was structurally normal.

The majority of the cases described were in children, who have no complaints, but their parents were anxious. Our patient had lived for many years unaware of his 2 fistulae, until 1 of them became infected.

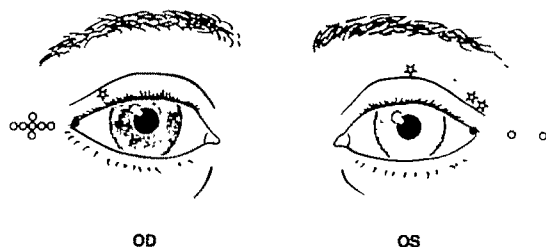


Fig. 4 All cases of congenital lacrimal gland fistulae found in the literature, together with our own case.

☆ Tarsal group with the orifice near the upper rim of the tarsal plate and with a tuft of hair. ○ Lateral group with the orifice near the external canthus and never with a tuft of hair. ● Both fistulae of our own patient.

drained from the palpebral part of the lacrimal gland. Whether the cystic enlargement on the left side is the cause or the result of the inflammation remains an open question. But it is obvious that the small diverticulae of the right fistula ran the risk of becoming inflamed as well. The x-ray descriptions of Schornstein,⁴ Frey,⁷ Damato,⁸ and Carpenter and Annamunthodo¹⁰ are similar to our findings.

Terlinck,² Malhotra,⁹ and Carpenter and Annamunthodo¹⁰ state that the fistula should be transplanted into the upper conjunctival cul-de-sac, and they report moderate success for their opera-

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Congenital crocodile tears: a key to the aetiology of Duane's syndrome

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SUMMARY The occurrence from birth of copious lacrimation on eating in some patients with Duane's syndrome suggests that both are caused by dysgenesis or a lesion in the vicinity of the abducens nucleus in the pons.

The legend that crocodiles wept before devouring their victims gave birth to the term 'crocodile tears' (gustolacrimal reflex) which is now used for the condition of copious lacrimation associated with eating. Reports of acquired crocodile tears frequently appear,¹ the symptom usually following traumatic or inflammatory conditions of the facial or greater superficial petrosal nerves. It is widely believed that the paroxysmal lacrimation results from the misdirection of regenerating parasympathetic secretomotor fibres subserving salivation. Reports of cases of congenital crocodile tears are rare. A summary of all reported cases (Table 1) shows that in all but the case of Antonelli, there is an associated abducens palsy or Duane's syndrome, and that in unilateral cases the lacrimal abnormality and eye movement disorder are ipsilateral, while in bilateral cases the movement disorder is also bilateral.

Duane's syndrome² was originally described as a musculofascial anomaly, but more recent studies based on electromyography^{3–7} suggest that the main feature is co-contraction of the horizontal eye muscles, which distinguishes Duane's syndrome from an abducens palsy. Retraction is often inconspicuous, and Huber *et al.*⁶ pointed out that co-contraction may be revealed only by electromyography. It is possible that cases described as having an abducens palsy have in reality a Duane's syndrome. The diverse associated anomalies referred to in Table 1 follow closely the pattern of anomalies described in Duane's syndrome by Sachsenweger,⁸ Kirkham,⁹ and Pfaffenbach *et al.*¹⁰ The occurrence of crocodile tears sheds some light on the causative lesion in Duane's syndrome.

Case reports

CASE 1

The child was a boy aged 3 years 4 months who

was the product of a normal pregnancy. Shortly after birth the parents had noted that there was no lacrimation from either eye when the child cried. From the time when solid foods were first taken, eating was accompanied by profuse lacrimation from both eyes. This had not been present on taking the bottle. No lacrimation occurred when soap or other irritants entered the eyes. From the age of 2 years there had been an increasing tendency for the eyes to move independently of one another on looking to the side. There was no relevant family history or past medical history. On examination, vision was 6/6 unaided in both eyes by the Sheridan Gardiner technique. There was a left, alternating convergent squint and a bilateral Duane's syndrome. Abduction was limited in each eye with retraction and upshoot of the adducting eye, and in addition adduction and convergence were slightly reduced. Investigation of the lacrimal defect confirmed abundant lacrimation on chewing a sweet. This was also present on chewing a tasteless rubber. Although corneal sensation was normal, no lacrimation was produced on stimulating the cornea with a cotton wool wisp or ammonia fumes.

General examination revealed a bland facial expression but normal emotional and voluntary facial movements. The distal phalanx of the little finger of each hand was markedly deviated towards the ring finger.

X-rays of skull and chest were normal. Eye movement recordings carried out by the Medical Research Council's Hearing and Balance Unit at the National Hospital, Queen Square, London, revealed that horizontal and vertical saccades could be generated in each eye in response to vestibular and optokinetic stimuli. Vestibulospinal reflexes were normal as judged by free-fall electromyography.¹¹ Stapedial reflexes were normal, indicating a normal innervation of the stapedius muscle by the facial nerve. The 5-tone audiogram was normal.

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Table 1 Summary of all reported cases

Case	Crocodile tearing	Emotional tearing	Facial weakness	Duane's syndrome or sixth nerve palsy	Other features
Antonelli ²⁴	Unilateral (R)	Absent			
Lutman ²⁴ 1	Unilateral (?R/L)	•	•	Unilateral (?R/L)	•
• 2	Bilateral	•	•	Bilateral palsy	•
3	Bilateral	•	•	Bilateral palsy	•
Lillie ²⁷	? Uni/bilateral	•	•	? Uni/bilateral palsy	•
D'Ermo ²⁶ 1	Bilateral	Absent	Absent	Bilateral Duane's	Oxycephaly, facial asymmetry
2	Unilateral (R)	Absent	Absent	Unilateral Duane's (R)	hypochromia iridis, facial asymmetry
Cricchi ²⁸	Bilateral	Absent	Absent	Bilateral Duane's	•
Jampel, Titone ²⁸	Unilateral (R)	Present	•	Unilateral palsy (R)	Anisometropia, skull bossing, syndactyly and arachnodactyly, scoliosis
Sarda <i>et al.</i> ⁴¹	Unilateral (R)	•	Absent	Unilateral palsy (R)	•
Rogenbogen, Stein ⁴²	Unilateral (L)	Present	Absent	Unilateral Duane's (R)	EMG features of Duane's syndrome
Uemura, Tamura ⁴³ 1	Bilateral	Absent	Absent	Bilateral Duane's	Bilateral deafness
2	Bilateral	Minimal	Absent	Bilateral Duane's	EMG features of Duane's syndrome
3	Bilateral	Minimal	Absent	Bilateral Duane's	
4	? Uni/bilateral	•	Absent	? Uni/bilateral Duane's	Supernumary auricle
Brik, Athayde ⁴⁴	Bilateral	•	Absent	Bilateral Duane's	Klippel-Fell anomaly
Trieschmann ⁴⁵ 1	Bilateral	Absent	Bilateral	Bilateral Duane's	Bilateral deafness, deformity of auricles
2	Bilateral (R>L)	Present	Unilateral (R)	Bilateral Duane's (R>L)	Deformity of auricles
Ramsay, Taylor 1	Bilateral	Absent	Moebius	Bilateral Duane's	Deformity of fingers
2	Bilateral	Absent	Moebius	Bilateral Duane's	Bilateral deafness, deformity of auricle

*Indicates that the presence or absence of the feature was not recorded.

CASE 2

The child, a boy aged 3 years 8 months when first seen, was the product of a full-term normal pregnancy. The parents had noted that from birth copious lacrimation occurred from both eyes on breast feeding. It continued after the child started taking solid foods. When eating dry foods he drank repeatedly. There had been no lacrimation from either eye when crying, and the parents were unaware of any eye movement disorder. He had been deaf from birth. There was no relevant family history or past medical history. On examination the vision was 3/6 in each eye by the Ffooks symbols. There was a small left, alternating convergent squint and a bilateral Duane's syndrome with marked limitation of abduction and slight retraction on attempted adduction in each eye. Adduction and convergence were reduced. Investigation of the lacrimal defect showed lacrimation on chewing a sweet or a tasteless rubber. Corneal sensation was normal, but no lacrimation was produced on stimulation of the cornea with a cotton-wool wisp or ammonia fumes.

General examination revealed a bland facial expression but normal emotional facial movements. Examination of the ears revealed a rudimentary right auricle and atresia of the right external audi-

tory meatus. The tympanic membrane could not be seen. The left auricle and external auditory meatus and drum appeared normal. There was response only to the loudest auditory stimuli, and it was felt that even this slight response might be to noise-induced vibration of the skull. There was a marked bilateral pes planus.

X-rays of skull, spine, and chest appeared normal. Eye movement recordings revealed a complete inability to generate horizontal saccades in either eye in response to vestibular or optokinetic stimuli. Small visually evoked vertical saccades could be generated but there was no vertical doll's head response. Vestibulospinal reflexes were absent on free-fall electromyography.

In these cases the features of bilateral abduction weakness and bland facial expression are suggestive of the Moebius syndrome. In case 2 the additional feature of a marked disturbance of vestibular mediated reflexes may be suggestive of a widespread lower brain stem disturbance.

Discussion

Two main theories have been advanced to account for the electromyographic feature of Duane's syndrome. One theory supported by Blodi *et al.*⁵

and Sato³ suggests that the defect lies at a supranuclear level, while the other supported by Hoyt and Nachtigäller¹² and Huber¹³ proposes that the defect is peripheral, there being a developmentally defective innervation of the lateral rectus by the abducens nerve with a variable pattern of innervation of the other ocular muscles.

The existence of a supranuclear pontine centre for lateral gaze was postulated by Crosby.¹⁴ Carpenter *et al.*¹⁵ suggested that in monkeys this centre is near or within the abducens nucleus. They showed that unilateral stereotactic destruction of the abducens nucleus was followed by gaze deviation to the opposite side. In the tissue studies of the same animals the preterminal degeneration was most marked in the contralateral medial longitudinal fasciculus and distributed preferentially to the ventral nucleus of the contralateral oculomotor nuclear complex (cells whose axons innervate the contralateral medial rectus). Similarly, Graybiel and Hartweig¹⁶ showed that ³H proline injected into the abducens nucleus of cats appeared within the contralateral ventral nucleus of the oculomotor nuclear complex. They proposed that these interneurons are the cells essential in conjugate lateral gaze. A theory that seeks to explain Duane's syndrome on the basis of a supranuclear lesion must therefore account for the normal action of the contralateral medial rectus.

The innervational theory suggested by Huber *et al.*⁶ and expanded by Hoyt and Nachtigäller¹² proposed that a maldevelopment of the abducens nucleus occurs, resulting in innervation of the lateral rectus by fibres of the oculomotor nerve, the variable electromyographic features reflecting the innervation of the lateral rectus by different branches of the oculomotor nerve. Unfortunately the anatomical evidence for substitute innervation is inconclusive, since no case of Duane's syndrome has been examined at necropsy with both histological examination of the brain stem and dissection of the nerves as far as the eye muscles.

The post-mortem study of a case of Duane's syndrome by Matteucci¹⁷ showed aplasia of the abducens nucleus. A case of bilateral abducens nerve palsy¹⁸ showed the absence of both abducens nerves with diminutive nuclei. Some anatomical support for substitute innervation has been drawn¹² from cadaver dissections (cases without information regarding eye movements in life) in which absence of the abducens nerve was associated with innervation of the lateral rectus by the oculomotor nerve.¹⁹⁻²²

However, these findings must be interpreted with caution. Svitzer²³ in cadaver dissections and Kimmel²⁴ in histological studies of embryo rabbits

have shown that 'anastomosis' between the oculomotor nerve and the abducens nerve sometimes occurs within the cavernous sinus and orbit. Absence of the abducens nerve in cadaver dissections must also be interpreted with caution. Kimmel²⁴ and Bremer^{25,26} showed that in some cases the fibres from the abducens nucleus do not emerge from the brain stem at the classical site. The innervation of the lateral rectus by a branch of the oculomotor nerve in the cadaver dissections of Generoli,¹⁹ Tillack and Winer,²⁰ Munnicks,²¹ and Fasebeck²² may reflect only an abnormal route by which abducens motoneurons reach their destination. In Tillack and Winer's case the abducens nucleus was reported as normal, which might be taken to suggest that although the 'abducens nerve' could not be found the motoneurons must have existed.

Bremer²⁶ suggested that absence of the abducens nerve might arise through a delay in the development of the ocular musculature, allowing the fibres of the abducens nerve to pass caudally, attracted by the postotic musculature. These fibres would disappear with the involution of the postotic mesoderm. Pfaffenbach *et al.*¹⁰ suggested that a teratogenic stimulus at an early stage of embryogenesis caused Duane's syndrome and its associated anomalies. Of 55 children with thalidomide embryopathy studied by Papst,²⁷ 4 had Duane's syndrome, and of those with eye movement disturbances many had facial pareses and ear deformities. He suggested that these disorders occurred between 34 and 39 days after the mother's last menstrual period. The other abnormalities associated with these cases of Duane's syndrome are comparable to those described by Pfaffenbach *et al.*¹⁰ Trieschmann²⁸ reported 3 patients with thalidomide embryopathy who showed crocodile tears, abducens nerve palsy, or Duane's syndrome and facial paresis, and 2 showed deformities of the pinnae of the ears.

If Duane's syndrome is of teratogenic origin the presence of crocodile tears in some cases sheds light on the site of the lesion. The close association of the eye movement disorder with the lacrimal disorder, respecting laterality in the unilateral cases and being bilateral in bilateral cases, suggests that a single teratogenic lesion is responsible for both. While the site of the lacrimal centre within the brain stem is uncertain, the similar embryological origin of lacrimal and salivary glands suggests that the centres controlling both lie in the same area. A centre controlling salivation exists in the lower brain stem, but its exact location is uncertain.

Kohnstamm²⁹ and Yagita and Hayama,³⁰ using the technique of retrograde degeneration, suggested a centre in the lateral reticular formation at the level of the facial nucleus. Using stereotactic

stimulation Magoun and Beaton³¹ in monkeys and Chatfield³² and Wang³³ in cats identified 2 areas in the lower brain stem that yield largely ipsilateral salivary secretion. They confirmed that salivation followed stimulation in the lateral area demonstrated by Kohstamm²⁹ and Yagita and Hayama,³⁰ but in addition a similar response was obtained from the dorsal paramedian reticular formation. Stimulating the intervening area of the reticular formation gave a limited response. Different interpretations were put on these findings. Chatfield and Wang thought that the salivary centre lay ventrolaterally near the facial nucleus and that secretion following stimulation in the dorsomedially placed area represented the stimulation of efferent fibres lying within the genu of the root of the facial nerve. Magoun and Beaton,³¹ however, felt that secretion produced by stimulation more laterally in the brain stem reflected the passage of efferent fibres from dorsomedial cells.

In the embryo rabbit Kimmel^{24,34} found a genu only in fibres from cells of the special visceral efferent column that contribute to the motor root of the facial nerve. This suggests that it is incorrect to ascribe secretion from stimulation in the dorsomedial area to stimulation of efferent neurones, and thus the interpretation of Magoun and Beaton³¹ seems more plausible, that is, that the salivary centre lies dorsomedially with efferents passing laterally through the reticular formation. A dorso-medial centre mediating parasympathetic function would not be surprising in view of the position of the Edinger-Westphal nucleus and the dorsal motor nucleus of the vagus. The cells lying rostrally in this dorsomedial column (that is, in closest association with the abducens nucleus) would subserve lacrimal secretion (indeed in the series of Magoun and Beaton 1 animal showed ipsilateral lacrimation on stimulation in this area).

The most logical explanation of the lacrimal and eye movement disorders in Duane's syndrome would be a lesion causing a nuclear degeneration or dysgenesis in the immediate vicinity of the abducens nucleus, the paradoxical aspects of Duane's syndrome and the lacrimal disorder being the result of a substitute innervation of the lateral rectus by fibres from the oculomotor nerve and the lacrimal gland by fibres subserving salivation.

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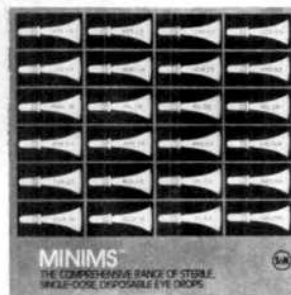
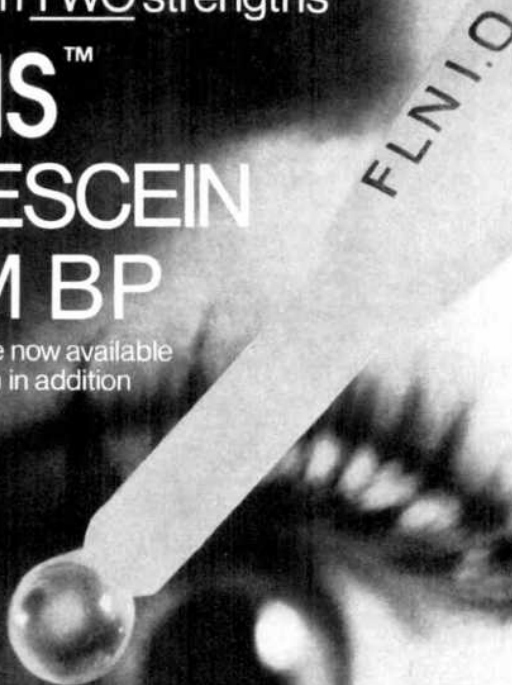


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Morphology of graft endothelium and donor age

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SUMMARY The corneal endothelium of 42 clear corneal transplants was studied with a specular microscope. The endothelial cell morphology was analysed by using a computerised image analysis system. A quantitative index was developed to study the degree of variation in cell size. By applying this objective index we observed that pleomorphism is independent of age, and considerable alteration occurs in cell morphology during healing.

The integrity of the corneal endothelium is the most critical factor in the successful outcome of a corneal graft.¹ Most of our knowledge of human corneal endothelial cell morphology is derived from studies of corneal buttons obtained at transplantation and from post-mortem eyes. The advent of clinical specular microscopy has made it possible to study the corneal endothelium *in vivo*. Previous studies on corneal grafts²⁻⁴ indicate a marked decrease in the endothelial cell density^{2,4} with increase in mean cell area.³ There is no correlation between either cell density or mean cell area and corneal thickness. From these observations it is apparent that neither cell density nor mean cell size is a decisive factor in the determination of corneal thickness.

The possibility exists that other aspects of endothelial cell morphology can influence graft survival. In the present study we photographed the endothelium of 42 clear corneal transplants using the specular microscope and studied the morphology of graft endothelium.

Materials and methods

Forty-two cases of clear corneal transplants were included in this study. The preoperative diagnosis for each case is listed in Table 1. In all instances the donor corneas were preserved in McCarey-Kaufman medium for less than 72 hours before use.

The endothelium was studied with a modified Syber clinical specular microscope. Photographs were taken and cell densities determined from at least 3 different photographic fields in each case, and the mean value was calculated. The methods

employed in the determination of cell density were described by Bourne and Kaufman.⁵ The central corneal thickness was determined by using a modified Haag-Streit pachometer at the time of specular microscopic examination. The intraocular pressure was also determined at the same time with a Langham type tonometer. The age of the donor is known in 37 of these cases. In 8 cases specular microscopy was performed on the donor corneas before preservation and transplantation. Statistical analyses were performed to correlate recipient and donor ages to the cell density of graft endothelium. A probability ratio of less than 0.05 (*t* test) was considered statistically significant.

A hand-outlined overlay in an 8×10 inch (20×25 cm) format was prepared from each photographic field by means of a pen with a felt tip of 0.35 mm width. The overlays were analysed by the Omnicon pattern analysis system. Data on area, perimeter, mean cell area, and standard deviation of cell areas were obtained.

We employed an index to quantify the degree of variation in cell size in a given cornea (polymegethism), which represents one aspect of the cellular pleomorphism. The index reflects the ratio of the standard deviation to the mean of the cell areas, and was calculated for each sample. This ratio, referred to as polymegethism quotient (PQ), is dimensionless, thus allowing direct comparisons between endothelial patterns regardless of cell size or population. The PQ approaches zero as the variation in cell size becomes minimal and reaches perfect uniformity.

Results

The pertinent clinical data for each patient included in the series are tabulated in Table 1.

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Table 1 Details of individual patients

Recipient age	Donor age	Postoperative duration (months)	Endothelial cell density (cells/mm ²)	Thickness (in mm)	Mean PQ	Rejection episodes	Preoperative diagnosis
80	55	9 mo	1066	0.44	0.302	No	Fuchs's dystrophy
80	14 mo	9 mo	3710	0.78	0.354	Yes	Aphakic bullous
77	65	8 mo	1422	0.60	0.228	No	Fuchs's dystrophy
73	13	1 mo	2800	0.68	0.355	Yes	Herpes simplex keratitis
71	10 mo	3 mo	3857	0.60	0.404	No	Aphakic bullous keratopathy
70	56	5 mo	2222	0.60	0.408	Yes	Fuchs's dystrophy
70	36	7 mo	1955	0.58	0.413	Yes	Fuchs's dystrophy
68	19	6 mo	800	0.76	0.357	No	Interstitial keratitis
67	46	5 mo	1244	0.63	0.497	Yes	Fuchs's dystrophy
67	60	3 days	2133	0.76	0.464	No	Fuchs's dystrophy
66	45	10 mo	1111	0.58	0.404	No	Fuchs's dystrophy
66	43	1 day	1689	0.78	0.344	No	Fuchs's dystrophy
65	59	8 mo	1422	0.62	0.366	Yes	Fuchs's dystrophy
64	58	2 mo	2266	0.74	0.673	No	Fuchs's dystrophy
63	33	4 mo	1156	0.68	0.350	No	Fuchs's dystrophy
63	25	1 wk	2488	0.62	0.450	No	Fuchs's dystrophy
62		3 mo	756	0.66	0.504	No	Herpes simplex keratitis
61	47	11 mo	1110	0.59	0.374	No	Fuchs's dystrophy
61	58	3 mo	1333	0.66	0.286	Yes	Keratitis sicca
61	48	2 mo	800	0.66	0.388	No	Corneal oedema
60	20	3 mo	3022	0.64	0.310	Yes	Graft failure
59	54	3 mo	1111	0.64	0.311	Yes	Corneal scar
58	52	1 mo	1818	0.70	0.365	No	Aphakic bullous keratopathy
57	30	22 mo	844	0.58	0.406	No	Keratoconus
55	57	3 wk	1906	0.64	0.576	No	Aphakic bullous keratopathy
55		1 day	2887	0.68	0.582	No	Fuchs's dystrophy
55	60	4 mo	1155	0.56	0.473	No	Fuchs's dystrophy
54		4 mo	1910	0.58	0.328	No	Fuchs's dystrophy
54	60	2 mo	800	0.52	0.306	No	Interstitial keratitis
51	52	6 mo	1910	0.64	0.507	Yes	Fuchs's dystrophy
48	36	6 mo	2399	0.58	0.400	No	Graft failure
47		2 mo	2043	0.66	0.323	No	Keratoconus
44	19	1 mo	1866	0.62	0.314	No	Keratoconus
39	62	3 wk	1511	0.54	0.371	No	Keratoconus
34		2 mo	800	0.66	0.386	No	Keratoconus
29	26	6 mo	1422	0.68	0.348	No	Keratoconus
28	60	11 mo	1333	0.80	0.248	Yes	Corneal oedema post-cong. glaucoma
26	17	2 mo	1995	0.62	0.396	No	Herpes simplex keratitis
25	15	1 mo	2860	0.66	0.531	No	Keratoconus
24	46	5 mo	2710	0.61	0.393	No	Corneal scar post-traumatic
21	65	4 mo	2044	0.50	0.422	No	Keratoconus
15	35	3 mo	1910	0.60	0.342	Yes	Corneal scar post-traumatic

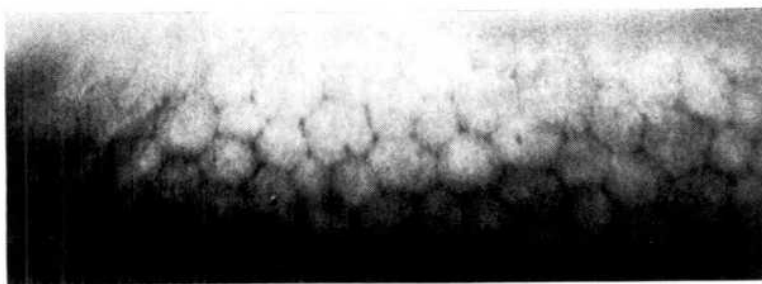


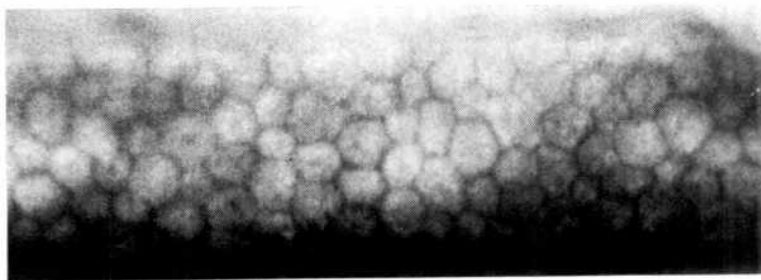
Fig. 1 Endothelium of the donor cornea obtained from a 52-year-old donor. Cell density 2128 cells/mm². Polymegethism quotient 0.288.

Fig. 2 Postoperative appearance of the graft endothelium 1 month after surgery at which donor cornea in Fig. 1 was used. Cell density 1818 cells/mm². Polymegethism quotient 0.365. Recipient age 58 years.



Fig. 3 Endothelium of the donor cornea obtained from a 15-year-old donor. Cell density 2860 cells/mm². Polymegethism quotient 0.445.

Fig. 4 Postoperative appearance of the graft endothelium 1 month after surgery at which donor cornea in Fig. 3 was used. Cell density 2533 cells/mm². Polymegethism quotient 0.480. Recipient age 25 years.



The endothelial cell density ranged from 444 to 3857 cells per square millimetre in this series. The cell density was found to have no correlation with corneal thickness. No correlation was observed between the cell density of the graft endothelium and the preoperative clinical status of the recipient cornea. Donor age was found to have an inverse correlation with cell density of the graft endothelium. No correlation was found between recipient age and cell density. In corneas where the donor tissue was obtained from adults, there was a decrease

in cell density during the postoperative period (Figs. 1, 2, 3, 4).

However, in the 2 corneas in which the donor ages were 10 and 13 months an increase in cell density was observed in the postoperative period. This increase was consistently apparent at each specular examination during the postoperative period (Figs. 5, 6, 7, 8) and is observed only in these 2 corneas.

Light microscopic examination of the pathological corneal buttons in the 2 cases in which infant

Fig. 5 Endothelium of the donor cornea obtained from a 14-month-old donor. Cell density 3187 cells/mm². Polymegethism quotient 0.182.

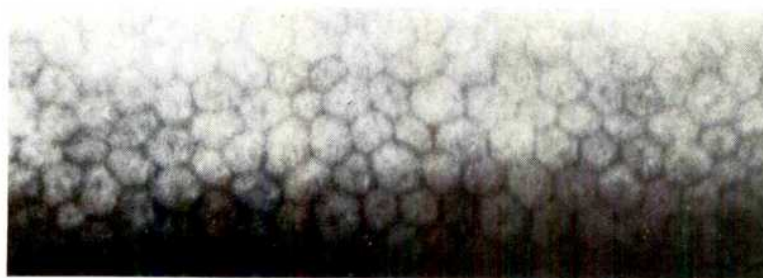
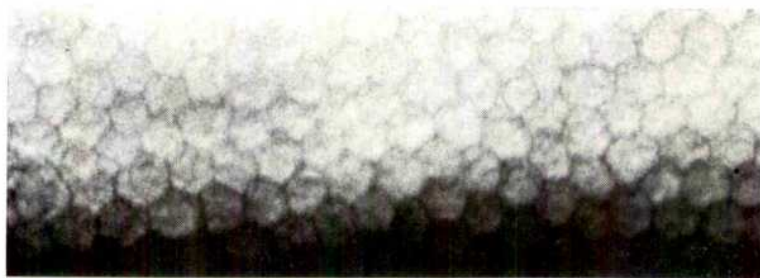


Fig. 6 Postoperative appearance of the graft endothelium 9 months after surgery at which donor cornea from Fig. 5 was used. Cell density 3710 cells/mm². Polymegethism quotient 0.312. Recipient age 80 years.

Fig. 7 Endothelium of the donor cornea obtained from a 10-month-old donor. Cell density 3200 cells/mm². Polymegethism quotient 0.316.

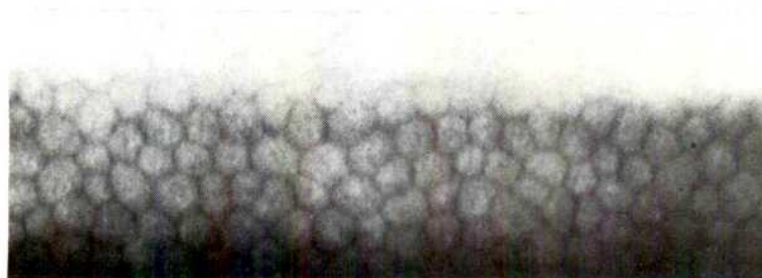
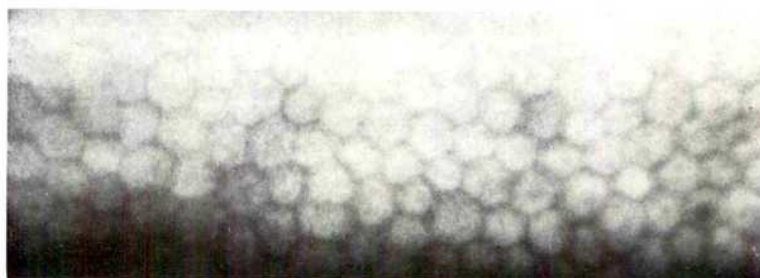


Fig. 8 Postoperative appearance of the graft endothelium 3 months after surgery. Cell density 3857 cells/mm². Polymegethism quotient 0.404. Recipient age 71 years.

corneas were grafted showed total absence of recipient endothelium. The preoperative clinical diagnosis in both cases was aphakic bullous keratopathy.

When we applied PQ to study the degree of variation in cell size to these 42 corneas, the value ranged from 0.179 to 0.673 with a mean of 0.389 (Table 1). We found no apparent correlation between the PQ and either donor or recipient age, indicating that pleomorphism is not influenced by age.

The results in Table 2 reflect the great alteration that occurs in corneal endothelium in the transition from donor to postoperative graft. The PQ values differed significantly between the donor endothelium and the graft endothelium.

Discussion

All corneas in the present study remained clear in spite of the wide variation in cell density. This clearly shows a lack of correlation between cell

Table 2 Alteration in corneal endothelium

Donor age	Donor endothelium		Graft endothelium	
	Cell density (per mm ²)	PQ	Cell density (per mm ²)	PQ
57	2527	0.411	1906	0.576
52	2128	0.288	1818	0.365
48	3059	0.554	800	0.388
17	2361	0.390	1995	0.396
15	2860	0.445	2860	0.480
13	3228	0.346	2800	0.355
14 months	3187	0.182	3710	0.354
10 months	3200	0.316	3857	0.404

density and corneal thickness and is in agreement with earlier reports.^{4,4}

Two cases in the present series showed an increase in cell density in the graft endothelium from that of the donor endothelium. This increase was evident in all postoperative specular microscopic examinations and is seen only in these 2 corneas. In both instances, the preoperative clinical diagnosis in the recipient was aphakic bullous keratopathy. The corneas were obtained from infant donors. This increase in cell density can only be explained by either a replication in the graft endothelium or the spread of cells from the recipient on to the graft. The total absence of corneal endothelium in the excised corneal buttons makes it very unlikely that the recipient endothelium has contributed to the increase in cell density. The morphological appearance of the graft endothelium is unlike that seen in patients with aphakic bullous keratopathy or in the normal corneas of the same age group. Although observations on a small sample of cases cannot be conclusive, the demonstration of an increase in cell density with time, in the endothelium of only these 2 corneas, strongly suggests the possibility of replication in infant corneal endothelium. However, confirmation of this phenomenon is possible only on histological examination.

The morphological appearance of the endothelial cells in these 2 grafts also supports the concept of persistence of the donor endothelium in the corneal graft. One of these cases was reported in an earlier publication.⁶

The study of pleomorphism and its role in corneal hydration has hitherto received very little attention. We examined this aspect of endothelial cell morphology by measuring the area of individual cells using an automated image analysis system.⁷ An index referred to as polymegethism quotient (PQ) was developed to quantitate the degree of variation in cell morphology in terms of variation in cell size. This represents our attempt to quantitate one aspect of pleomorphism.

When we applied this index to the present series of cases, certain interesting observations emerged. The lack of correlation between PQ and either donor or recipient age contradicts earlier observations, which indicate an increase in pleomorphism with advancing age.⁸⁻¹⁰ The precision and the objectivity of the methods used in this study were lacking in the previous reports. The other striking feature that has come to light is the dynamic alteration that occurs in endothelial cell morphology in the transition from donor endothelium to graft endothelium.

Our observations in the present study make it apparent that endothelial cell morphology of corneal grafts presents a great degree of variability.

PQ is a dimensionless ratio developed from measurements of cell areas by the application of a mathematical relationship. A dimensionless ratio is independent of cell size, cell density, and the age of the patient. Thus, the PQ index offers the opportunity to analyse objectively endothelial cell morphology per se in our efforts to quantitate the changes which occur during the healing process.

A comprehensive analysis of all morphological parameters is essential to understand fully the role of endothelial cell morphology in corneal transparency, and to study objectively the healing processes in the corneal endothelium.

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Athalamia as a late complication after keratoplasty on aphakic eyes

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SUMMARY In 3 cases of keratoplasty in aphakic eyes 4–8 months after surgery a gradual flattening of the anterior chamber was observed. During the initial postoperative months there was no suggestion of any impending complication. No synechiae at the anterior chamber angle were present, the anterior vitreous face had remained intact without being in contact with the posterior corneal surface, and the intraocular pressure remained within normal limits. Separation of anterior synechiae as well as vitrectomy via pars plana resulted merely in a temporary amelioration of this condition. Within a few days the anterior chamber was abolished again. The corneal buttons displayed epithelial oedema; the deeper layers, however, remained clear. Development of secondary glaucoma was kept under control either by appropriate medication or by cyclocryotherapy. The phenomenon reported here developed only in cases in which the anterior vitreous face had remained intact. It seems possible that this type of late complication may be avoided by prophylactic vitrectomy.

Whereas until a few years ago there was uncertainty whether a 2-stage operation or a combined operation was preferable in cases of corneal opacity and cataract, today the 1-stage combination of keratoplasty and cataract removal has largely prevailed. Fine¹ has alluded to the high probability of clouding of the transplant if the vitreous touches the posterior surface of the cornea. A number of authors have tried to develop a method to keep the anterior chamber free of vitreous.^{1–6} The main object is to ensure an intact anterior hyaloid membrane. As in the case of conventional cataract surgery, this is actually possible with appropriate hypotony even with a wide opening of the eyeball after trephination of the cloudy host cornea. But if the hyaloid membrane ruptures, and vitreous enters the anterior chamber, an anterior vitrectomy is advisable.

So far the results of perforating keratoplasty and simultaneous cataract extraction can be compared with those of keratoplasty on phakic eyes. Sautter⁷ records irreversible clouding of transplant in only 8% of cases. Arentsen,⁸ Capella,⁹ Kaufman,¹⁰ and Meyer¹¹ have obtained clear transplants in 70–80% of their cases. The most frequent postoperative complication in the combined procedure as well as in keratoplasty in aphakic eyes is ocular hypertension.^{10,12} Olson¹² points out that this is not unusual

even in patients who had normal tension preoperatively. He comes to the conclusion that virtually only those patients in whom preoperative glaucoma could be ruled out, or those whose tension did not exceed 27 mmHg in the first postoperative week, have no protracted tension problems. Kaufman¹⁰ attributes postsurgical rise of tension to a pupillary block caused by vitreous hernia.

Most authors therefore suggest one or more peripheral iridotomies or iridectomies, as is usual in conventional cataract operations. Zimmerman and Olson¹³ found a significant decrease in frequency of postoperative rise of tension in those cases in which the diameter of the donor cornea has exceeded that of the host flap by 0.5 mm on an average.

Patients and methods

During postoperative follow-up of patients on whom we had undertaken combined cataract-keratoplasty surgery or a corneal transplant for aphakia during the past 2 years we noticed a phenomenon which is not comparable to any reported observation on this subject. In 3 patients we detected about 4–8 months postoperatively an advancing flattening of the anterior chamber. During the first few months after surgery the postoperative course was essentially inconspicuous. There were no goniosynechiae, the intact anterior hyaloid membrane had no contact with the cornea, and tension was within the normal

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range. We have therefore searched our files of patients operated on within the past 2 years in order to discover from the surgical notes and the notes on the postoperative course a pointer to the cause of this phenomenon. Of the 72 perforating keratoplasties performed during this period 7 were done on aphakic eyes. In 9 cases corneal grafting was combined with cataract extraction. Anterior vitrectomy was necessary in 4 aphakic eyes, and twice during combined procedure.

CASE 1

Female, born 4 February 1896. Bilateral cornea guttata, iridoschisis in the inferior nasal quadrant, and nuclear cataract. 24 October 1974: Cryoextraction of lens in the right eye with total iridectomy. No complications in the vitreous. Postoperative development of a therapy-resistant bullous keratopathy with adhesions of the anterior iris layer with thickened cornea in the region of iridoschisis. These adhesions were separated on 22 April 1975 and the anterior chamber was filled with Ringer's solution. 12 January 1977: perforating keratoplasty right eye (7.0/7.1 mm diameter). Anterior hyaloid membrane remained intact. The case healed initially without complications, the graft remained clear, the anterior chamber was deep, and even in the area of iridoschisis there was no corneal contact. On 13 May 1977 the anterior chamber had disappeared peripherally, and a flat chamber was present only at the centre. The corneal graft showed epithelial oedema, tension 27 mmHg. Over the next few weeks the anterior chamber flattened completely. Owing to the poor general health of the patient no further surgical intervention was undertaken. The intraocular tension could be controlled satisfactorily with 2% Piladren (pilocarpine 20 mg and adrenaline 20 mg per ml) drops thrice daily, and thereafter the graft remained clear. On 23 August 1978 the patient had vision 6/12, Jaeger 3-4, with contact lens.

CASE 2

Female, born 15 September 1905. Bilateral corneal scars following eczematous keratitis mainly in the right eye and anterior and posterior cortical cataract. 26 April 1974: cryoextraction of cataract left eye. 24 January 1977: perforating keratoplasty (7.0/7.1 mm diameter) and cryoextraction of cataract right eye; the anterior hyaloid membrane remained intact. 17 August 1977: removal of running Tübingen-suture. At postoperative examination on 12 September 1977, the anterior chamber was flattened peripherally, one week later completely. The graft remained clear. 20 September 1977: separation of synechiae and air injection into anterior

chamber. After absorption of the air bubble, the anterior chamber flattened again; dilatation of the pupil by mydriatics showed posterior synechiae to the vitreous. 11 October 1977: vitrectomy through pars plana with the Klöti-vitreophage and air injection into the anterior chamber, the latter, however, flattening shortly thereafter. Because of raised intraocular pressure cryopexy was performed twice during the following months; the tension, however, could not be controlled satisfactorily. Finally the graft was cloudy, somewhat oedematous, and the anterior chamber was abolished. Vision was reduced to doubtful light projection and perception of hand movements close to the eye.

CASE 3

Female, born 28 December 1901. Mature cataract left eye, nuclear cataract right eye, bilateral cornea guttata. 16 November 1976: cryoextraction of cataract left eye, postoperative development of a therapy resistant bullous keratopathy; on 18 February 1977 a perforating keratoplasty (7.0/7.5 mm diameter) was performed. The anterior hyaloid membrane remained intact. Postoperatively the graft was clear and the anterior chamber deep; the intraocular tension remained normal. On 25 May 1977 the anterior chamber had flattened, anterior synechiae were not present. On 20 June 1977 the anterior chamber existed only in the pupillary area, the iris lay close to the posterior corneal surface circularly, the vitreous had no corneal contact. 21 June 1977: posterior sclerotomy was performed, anterior synechiae were separated and the anterior chamber was filled with Ringer's solution. A few days later the anterior chamber was flattened again. The tension could be regulated to some extent by cyclocryopexy. 25 August 1977: vitrectomy via pars plana with the Klöti-vitreophage, separation of anterior synechiae, and filling of anterior chamber with Ringer's solution. Thereafter the anterior chamber stayed only for a few days. A cyclodialysis and a renewed cyclocryopexy effected no enduring success. Finally, vision was reduced to perception of hand movements close to the eye and deficient light projection. The graft showed epithelial oedema; stroma was clear.

Discussion

Anterior synechiae, particularly goniosynechiae accompanied by secondary glaucoma in aphakic eyes after corneal grafting, are not unusual. A likely cause would be retrocorneal membranes forming after destruction of endothelial cells of the cornea¹⁴ or occasionally epithelial invasion.¹⁵ Böke¹⁶ observed anterior synechiae mostly in cases of

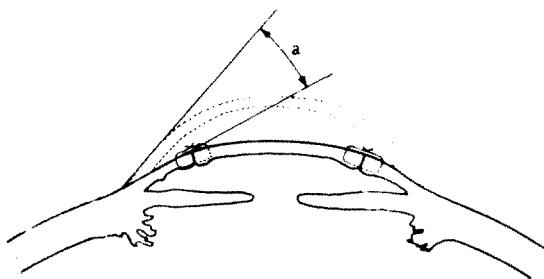


Fig. 1 Change in corneolimb angle (a) after penetrating keratoplasty when using same size donor button as recipient bed¹⁸

recurring inflammation, as in herpetic keratitis or if the keratoplasty was accompanied by loss of vitreous. In our cases we saw similar anterior synechiae after anterior vitrectomy; however, these adhesions were separable and did not show a tendency to indirect athalamia.

Zimmerman and Olson^{13,17} developed a mathematical model which depicts the relationship between the technique of a keratoplasty and the width of the chamber angle (Fig. 1). Accordingly, large grafts, small donor corneas, and extensively and closely placed sutures¹⁸ lead, through gathering up of the tissues, to a narrowing of the chamber angle, provoking the liability to secondary glaucoma. The authors suggest that the structures of the irido-corneal chamber angle are held stable by an anterior and posterior support mechanism. Anteriorly Descemet's membrane and the line of Schwalbe and posteriorly the lens, the zonule fibres, and the ciliary body seem to be a prerequisite for the maintenance of the chamber angle.

As by combined cataract keratoplasty surgery both supporting mechanisms are involved, one can imagine that aphakia may promote the development of a secondary glaucoma after keratoplasty. With this concept of diminution of the anterior segment of the eye in mind one can also explain the slow increase of flattening of the anterior chamber which could be observed in our cases. The solid vitreous body firmly fixed to the vitreous base can shift only within limits into the subvitreal fluid area in cases of posterior vitreous detachment. The iris diaphragm rests on the anterior hyaloid membrane with far more tension than in a case of simple aphakia. The aqueous flow to the anterior chamber is impeded despite iridectomy, which usually cannot be made

quite peripherally in the course of combined keratoplasty cataract operation. Finally adhesions between iris and vitreous could further increase the resistance of outflow. The phenomenon of post-operative flattening and abolition of the anterior chamber of aphakic eyes after keratoplasty was exclusively encountered in cases in which the anterior hyaloid membrane remained intact during the operation. It is conceivable that this late complication might not have occurred after a preventive anterior vitrectomy. Further studies of that possibility are indicated.

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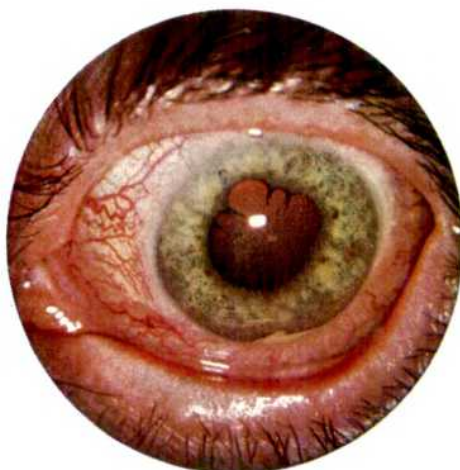
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Fish hook injuries of the eye

R. S. BARTHOLOMEW AND MARGARET MACDONALD

From the Department of Ophthalmology, University of Edinburgh

SUMMARY Two cases of fish hook injuries to the eye are described. Both were removed successfully by rotating the hook through undamaged tissue before snipping off the barb. Good vision was restored without complications for periods of 12 and 18 months.

A barbed fish hook embedded in the eye is an injury unlikely to be forgotten by any ophthalmic surgeon. Reported incidents of this kind are rare, however.^{1,2} Two such cases are described in this paper. In both our patients the injury was caused by a 3-pronged steel salmon hook, one of the prongs with its barb penetrating the globe.

Fish hook injuries most commonly occur in the hand. The standard method used to remove them from this site is to push the barb out through the skin, snip it off, and then rotate the shaft backwards along the entry path.³ If the hook is simply dragged backwards with the barb in situ it produces much greater soft tissue damage.

We decided to remove the hooks in our patients by this method, as they were so large.

Case reports

CASE 1

A man aged 39 was casting for salmon. His line was deflected by small twigs, and the hook embedded itself in his right eye. He cut off the line but made no attempt to remove the hook.

On examination (Fig. 1) one of the prongs was seen to have penetrated the cornea, injuring the iris and lens. Under general anaesthesia the hook was rotated so that the intraocular barb emerged through the angle, counter pressure being applied each side of the exit wound. The barb was snipped off with wire cutters and the shaft then removed through the entry wound.

The traumatic cataract was aspirated 36 days later and a soft contact lens fitted. Eighteen months after injury the eye was free from complications and had regained 6/9 vision (Fig. 2).



Fig. 1 Case 1: barb piercing central cornea

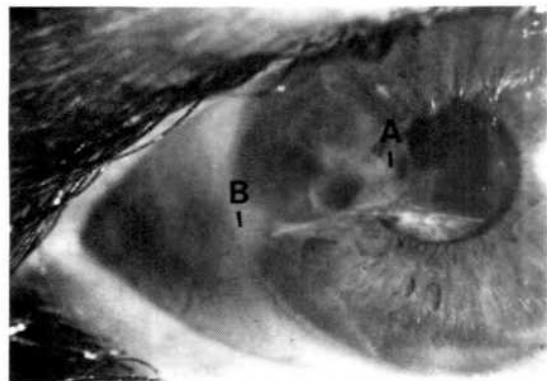


Fig. 2 Case 1: 12 months after injury, entry wound in central cornea A, exit wound at limbus B

CASE 2

A man aged 21 was rowing a boat for salmon fishermen when a hook cast by one of them caught in his left eye. No attempt was made to remove it but the line was cut off.

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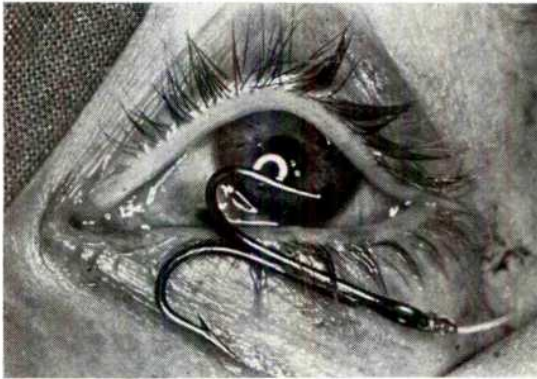


Fig. 3 Case 2: barb piercing nasal ciliary body

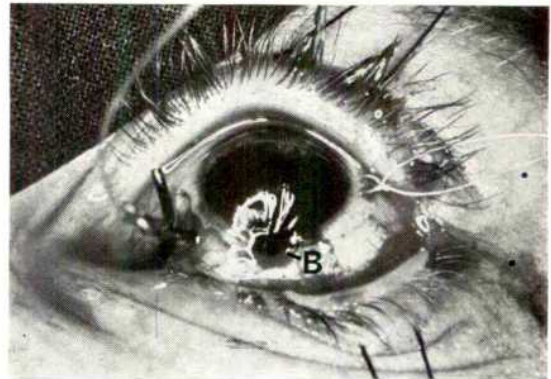


Fig. 4 Case 2: entry and exit (B) wounds before removal of hook

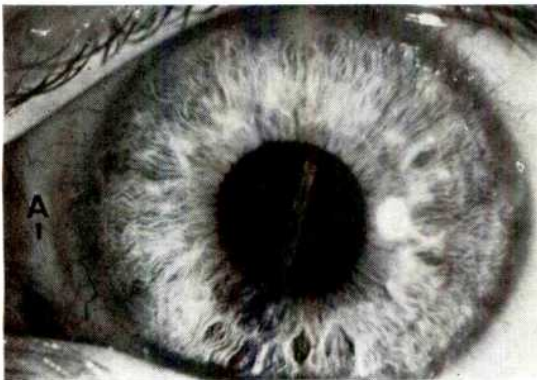


Fig. 5 Case 2: 3 months after injury, entry wound in sclera A, exit wound in peripheral cornea at 6 o'clock

On examination one of the prongs had penetrated the sclera over the nasal ciliary body, and the barb lay in the posterior part of the lens (Fig. 3). Under general anaesthesia the barb was rotated to emerge just behind the iris at 6 o'clock (Fig. 4). Prior to this manoeuvre the 2 extraocular barbs were amputated, as their position made the manipulation difficult. Tin snips were used to remove the 3 barbs, as steel wire cutters proved ineffective in this case. Removal of the shaft was then completed through the entry wound.

The traumatic cataract was aspirated 45 days later and a soft contact lens fitted. Twelve months after injury, there were no complications and the visual acuity was 6/9 (Fig. 5).

Discussion

Large intraocular foreign bodies are associated with a poor prognosis.⁴ The hooks removed from our patients' eyes were large (Figs. 1, 3, 5, and 6), but

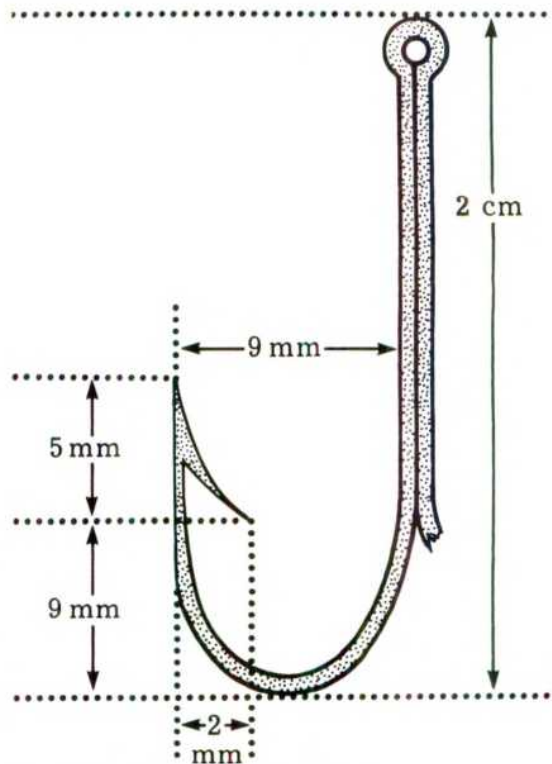


Fig. 6 Diagram of no. 4 salmon hook

the eventual visual results were good. The appearance of an eye with such a hook embedded in it is daunting to patient and surgeon alike, but removal by the method outlined in this paper is fairly simple and in our 2 cases has not led to any complications.

The manoeuvre of pushing the hook out through the eye is the same movement used in manipulating

a curved suture needle and is one familiar to all surgeons. If technically possible it would seem best to push the hook out through the peripheral cornea as described in one of the cases reported by Lugli and Vallavanti,¹ but in neither of our cases was this feasible, and no complications arose as a result of the exit wound being made in the region of the iris root. The shaft of the hook should be left long to facilitate manipulation. The extraocular barbs may have to be removed; powerful steel cutters are therefore essential.

We are grateful to Colin Hood, photographer, University of Edinburgh for the illustrations, and to Dr H. B. Chawla, consultant ophthalmologist for permission to report case 2.

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Ophthalmoplegic migraine and aberrant regeneration of the oculomotor nerve

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SUMMARY A patient with ophthalmoplegic migraine developed aberrant regeneration of the oculomotor nerve. This finding supports the view that the oculomotor nerve lesion in ophthalmoplegic migraine is peripheral, but its rarity suggests that the underlying mechanism may be ischaemic rather than compression by an oedematous intracavernous internal carotid artery.

Ophthalmoplegic migraine was first described by Charcot in 1890.¹ In a typical case there is a long history of recurrent attacks of unilateral headache over many years prior to the headache being associated with ophthalmoplegia. The pain is usually more severe and protracted than in other forms of migraine, and after several days an ipsilateral oculomotor paralysis develops which may last from hours to many weeks. Less commonly the trochlear and abducens nerves have been involved. The attacks of extraocular muscle weakness become more severe with each attack until a permanent unilateral oculomotor palsy develops.²

The site of the lesion of the oculomotor nerve in ophthalmoplegic migraine was regarded as being in the cavernous sinus by Walsh and O'Doherty³ after the observation of a constricted intracavernous internal carotid artery on angiography in 2 patients. The mechanism whereby cranial palsies occurred was postulated to be a compression of the nerve by the oedematous carotid arterial wall.

Aberrant regeneration of the oculomotor nerve is seen during the recovery phase from acute palsies produced by aneurysms and head injury and rarely by tumours. In children it is common sequel to a congenital third nerve palsy.⁴ The same disorder has been reported in the absence of an acute oculomotor palsy in patients who were subsequently shown to have meningiomas of the cavernous sinus.⁵ We report the case of a patient with ophthalmoplegic migraine who developed aberrant regeneration of the oculomotor nerve.

Case report

A 45-year-old man was in good health until 1970,

when he began to suffer from recurrent episodes of severe headaches associated with ophthalmoplegia. The headaches occurred at about 6-monthly intervals and were throbbing in nature. They began gradually over the right orbit and radiated back into the right occiput. They were associated with nausea and vomiting and resulted in his admission to hospital on at least 4 occasions. Typically the headaches would gradually increase in intensity over 4 days and then quickly subside after the onset of double vision. There was no previous history of headaches suggestive of migraine, nor family history of migraine. He sustained 8 episodes of complete right third nerve palsy, 2 of which were associated with fourth and sixth nerve palsies. The ocular palsy always involved the right eye, lasted 2 to 6 weeks, and was followed by a complete recovery of function.

In December 1976 painful ophthalmoplegia developed with involvement of the right third nerve. Six weeks later, when the patient's eyelids began to open, he noted blurred vision for near. On examination at that time he displayed typical features of a right third nerve paresis with aberrant regeneration. A right partial ptosis was present in the primary position with eye lid retraction in downgaze (Figs 1, 2, 3). There was a limitation of all movements of his right eye except abduction and intorsion. On attempted adduction and depression of the right eye, with distance fixation his right pupil constricted. In the primary gaze position his right pupil was mid-dilated and unresponsive to light. The general examination was normal and there were no other neurological abnormalities.

Skull x-rays and right carotid arteriography were normal. Cerebrospinal fluid examination, including VDRL, full blood examination, fasting blood sugar, and erythrocyte sedimentation rate were all normal.

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Fig. 1 Right partial ptosis in the primary position.



Fig. 2 Retraction of right upper lid on downward gaze.



Fig. 3 Failure of adduction of the right eye on gaze to the left.

The clinical features of this patient are typical of ophthalmoplegic migraine apart from the absence of a history of migraine before the onset of the attacks of ophthalmoplegia. The painful ophthalmoplegia seen in diabetes mellitus was ruled out by blood sugar estimations, and carotid angiography excluded the presence of an aneurysm of the internal carotid artery or posterior communication artery. There was no evidence of neurosyphilis or other local infections.

Discussion

An important cause of recurrent painful ophthalmoplegia is the Tolosa-Hunt syndrome,⁶ which must be included in the differential diagnosis of ophthalmoplegic migraine. In this condition the pain, which usually lasts more than several days, may precede the ophthalmoplegia, and is described as a steady boring pain rather than a throbbing hemicrania. The neurological involvement is usually more extensive than in ophthalmoplegic migraine and has included involvement of the optic, oculo-

motor, trochlear, ophthalmic division of the trigeminal, abducens, and ocular sympathetic nerves. In addition there may be proptosis greater than that which would be simply attributed to an oculomotor palsy. The condition is recurrent, with spontaneous remission, and may alternate from one side to the other. The aetiology is unknown and in the few cases, in which the pathology has been studied the lesion involving the cavernous sinus has been reported as nonspecific granulomatous tissue.⁷ As in ophthalmoplegic migraine, carotid angiography in the Tolosa-Hunt syndrome has shown arterial narrowing in the cavernous sinus, but in addition the superior orbital veins have also been occluded.⁸ In our own experience computerised axial tomography of the orbit in the Tolosa-Hunt syndrome has shown areas of increased density in the apex of the orbit which also enhanced with contrast media, and it is of interest that similar changes have been reported in orbital pseudotumour.⁹ Hallpike has suggested that Tolosa-Hunt syndrome and orbital pseudotumour have pathological features in common.

It seems unlikely that our patient has had the Tolosa-Hunt syndrome in view of the large number of recurrences, their relatively stereotyped and unilateral nature, and the absence of involvement of other structures in the superior orbital fissure and orbital apex. The patient was not given corticosteroids at any stage. Although a prompt remission of pain followed by recovery of the deficit is an essential diagnostic criterion for the Tolosa-Hunt syndrome, steroids might be effective in ophthalmoplegic migraine, since their value in migrainous neuralgia has recently been described.¹⁰

Aberrant regeneration of the oculomotor nerve implies that there has been interruption of the axons with subsequent regrowth which has been misdirected. The signs of aberrant regeneration of the oculomotor nerve were confirmed in this patient

by the presence of ipsilateral eyelid retraction on downward gaze and constriction of the pupil on attempted adduction and depression of the affected eye. These 2 characteristics are the result of axons intended for the inferior rectus growing into the branch to the levator and those for the medial and inferior rectus being misdirected to the pupil. The third feature of a typical case was not seen, namely, the adduction of the affected eye on attempted elevation or depression due to misdirection of fibres from superior and inferior rectus into the medial rectus.

Walsh and Hoyt¹¹ noted that they had not observed aberrant regeneration of the third nerve in ophthalmoplegic migraine but they were aware of a single case. The fact that it does occur implies in some instances partial disruption of the nerve fibres of the peripheral or extra-axial portion of the oculomotor nerve during attacks. However, one would expect a higher incidence of aberrant regeneration if the lesion in ophthalmoplegic migraine were due to compression by an oedematous intracavernous section of the internal carotid artery. In addition one might expect a much higher incidence of sixth nerve palsy in view of its closer anatomical relationship to the artery. The rarity of aberrant regeneration of the oculomotor nerve in ophthalmoplegic migraine is akin to its rarity in diabetic oculomotor palsies, of which Walsh¹² reported only 4 cases. Unlike diabetes, in which pupillary involvement in oculomotor palsies is unusual, internal ophthalmoplegia is commonly seen in ophthalmoplegic migraine. The pathology of the diabetic lesion has been established by Dreyfus *et al.*¹³ and Asbury *et al.*¹⁴ who demonstrated demyelination of the central axons of the nerve, which they concluded, on the basis of severe hyaline degeneration of the intraneural arterioles, was ischaemic in origin. The frequent sparing of the pupil is attributed to the peripheral position of the parasympathetic fibres in the superior aspect of the oculomotor nerve.¹⁵

The oculomotor nerve receives its blood supply in the cavernous sinus mainly from branches of the tentorial artery, which is one of 3 divisions of the meningo-hypophyseal trunk, the principal branch of the intracavernous carotid artery.¹⁶ Asbury *et al.*¹⁴ also found that the nerve was supplied in its anterior portion by recurrent branches from the ophthalmic artery and in its posterior intracavernous course from the circle of Willis by small vessels arising from the posterior communicating and posterior cerebral arteries.

As an alternative explanation to direct compres-

sion of the oculomotor nerve by an oedematous intracavernous carotid artery in ophthalmoplegic migraine Walsh and O'Doherty³ also suggested interference with the vasa nervorum of the nerve by the oedema. Walsh and Hoyt¹¹ extended this concept to include occlusion of the ostia of the small arterial branches of the intracavernous carotid artery. The fact that aberrant regeneration of the oculomotor nerve does occasionally occur in migraine confirms that the lesion is in the peripheral portion of the nerve, and it is postulated that its relative rarity makes direct compression with resultant mechanical distortion by the internal carotid artery unlikely. Further it seems likely that the lesion is primarily ischaemic and due to occlusion of the numerous small vessels which supply the nerve in the region of the cavernous sinus, either by direct spasm or by oedema closing their ostia in the internal carotid artery.

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Ultrastructure of fenestrations in endothelial choriocapillaries of the rabbit—a freeze-fracturing study

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SUMMARY Replicas of freeze-fractured endothelial cells of normal rabbits' choriocapillaries were studied. Differences in fenestral appearance on the E face and P face could be detected. E face pores appeared as circular craters containing particulate material arranged at the pores' rim and a central diaphragm. Mean pore diameter was 78.5 nm, average diaphragm size 30 nm, and peripheral particle size 12.3 nm. In several pores possible radiating connections between diaphragm and peripheral particles could be observed. Pores in the P face appeared as vallate papillae, with a circular, particulate, elevated rim surrounding a shallow surface and a central accumulation of particles resembling the diaphragm. The diameter of P face pores was found to be 76.5 nm, with a diaphragm size of 23.7 nm, and peripheral particle size of 12.7 nm. The calculated space between peripheral particles and diaphragm was 12.0 nm for the E face and 12.7 nm for the P face. With the Markham method a regular pattern of 8 peripheral particles at the pores' rim was observed on both E face and P face. A possible 3-dimensional model of the choriocapillary endothelial fenestration is presented. This model consists of 8 peripheral particles which are connected with a central diaphragm creating a space of 12.0-12.7 nm between them. This sieve-like structure and the calculated passage size fit well with the 'small pore' theory of molecular permeability.

A knowledge of the structural and physiological aspects of the choroidal endothelial fenestration is essential for understanding macromolecular permeability to the external retina. In the choriocapillary endothelium transmission electron microscopy studies have shown a diaphragm in the centre of the pore in cross and tangential sections.¹⁻⁴ This finding was reconfirmed by other investigators using the freeze-fracture technique.^{5,6} More thorough ultrastructural studies of the pores were carried out on fenestrae in other organs, such as kidney, pancreas, and intestinal tract.⁷⁻¹⁰ Maul,¹⁰ studying the rat kidney, suggested an octagonal shape for the pores' rim, and assumed that the central diaphragm consists of 2 rings. Clementi and Palade¹¹ showed that peroxidase molecules, about 5 nm in size, could pass more freely through the intestinal fenestrae than ferritin molecules, 11 nm in size.

Bill¹² showed that uveal capillaries are more permeable to myoglobin (4 nm) than to albumin (7 nm) and to albumin more than to gammaglobulin (11 nm). The aim of this study was to determine whether the intrafenestral ultrastructure can be correlated with the special permeability properties of the choriocapillaries.

Materials and methods

Four albino rabbits of 2.5-3.0 kg body weight were anaesthetised with 30 mg/kg pentobarbitone sodium injected intravenously. After deep anaesthesia was achieved one eye of each rabbit (4 eyes) was enucleated; other eyes were used for another study. The enucleated globes were cut in 0.1 M cacodylate buffer. The retina was gently stripped from the choroid, and then the choroid was carefully removed from the sclera. The choroidal tissue was immediately immersed in a solution of 2.5% glutaraldehyde in 0.1 M cacodylate buffer and fixed at 4°C overnight. After fixation the samples of tissue were

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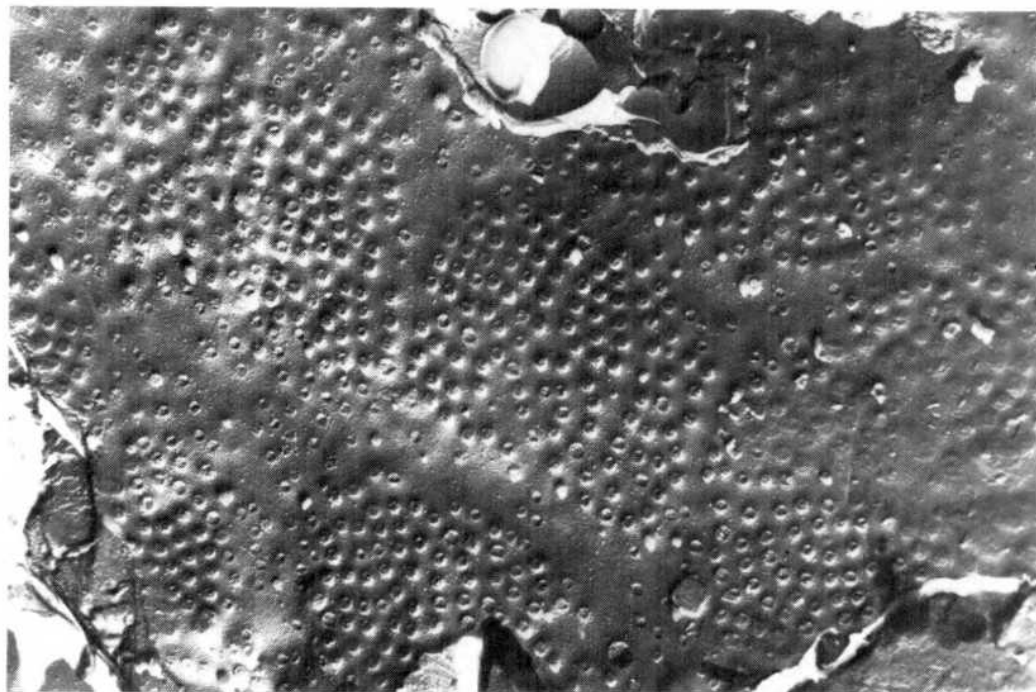


Fig. 1 Freeze-fractured replica of endothelial cell membrane showing groups of fenestrations separated by smooth cytoplasmic areas. ($\times 24\,000$).

washed several times with cacodylate buffer and suspended overnight in 30% glycerol in the same buffer at 4°C. Samples 2–3 mm in size were frozen in Freon 22, transferred immediately to liquid nitrogen, and freeze-fractured in a Balzer's freeze-etching unit, according to the standard procedures.¹³ All preparations were examined and photographed in a Jeol-100B electron microscope at 80 kb.

Results

In the replicas of freeze-fractured tissue the choriocapillaries were easily identified because of their proximity to Bruch's membrane and the characteristic appearance of the fenestrae. In surface view of the endothelial cell groups of closely packed fenestrations were separated by nonfenestrated, relatively smooth cytoplasmic areas. Most of the fenestrae observed were circular; some which were cleaved obliquely had an oval rather than circular shape (Fig. 1).

At higher magnifications the differences between fenestrae exposed in different split membranes were more evident. On the E face¹⁴ the pores appeared as circular craters containing particulate material arranged at the pores' rim and a central

diaphragm. The diaphragm appeared either as a smooth face or as a cluster of small particles, the appearance presumably depending on the cleavage plane. The peripheral particles seemed to be regularly arranged close to the rim in many fenestrae, especially in those cleaved tangentially. Structures which looked like radiating rays could be observed in some pores, connecting the peripheral particles with the central diaphragm (Fig. 2). On the P face the fenestrae appeared as vallate papillae. They seemed to be protruded, with a circular raised, particulate rim surrounding a shallower surface. In the crater a cluster of particles resembling the diaphragm could frequently be observed (Fig. 3).

A histogram of 120 pores has been drawn recording the fenestral diameter, peripheral particle size, and diameter of the diaphragm. Measurement of the diaphragm diameter presented some difficulty because of the inconsistency in appearance of the diaphragms due to differences in the cleavage plane. Consequently the measurements were either of the smooth central area or of the diameter of clustered particles. Of the 120 pores measured 48 were on the E face and 72 on the P face. Only circular, regular, tangentially cleaved pores were selected for measurement. Measurements of the fenestrae and

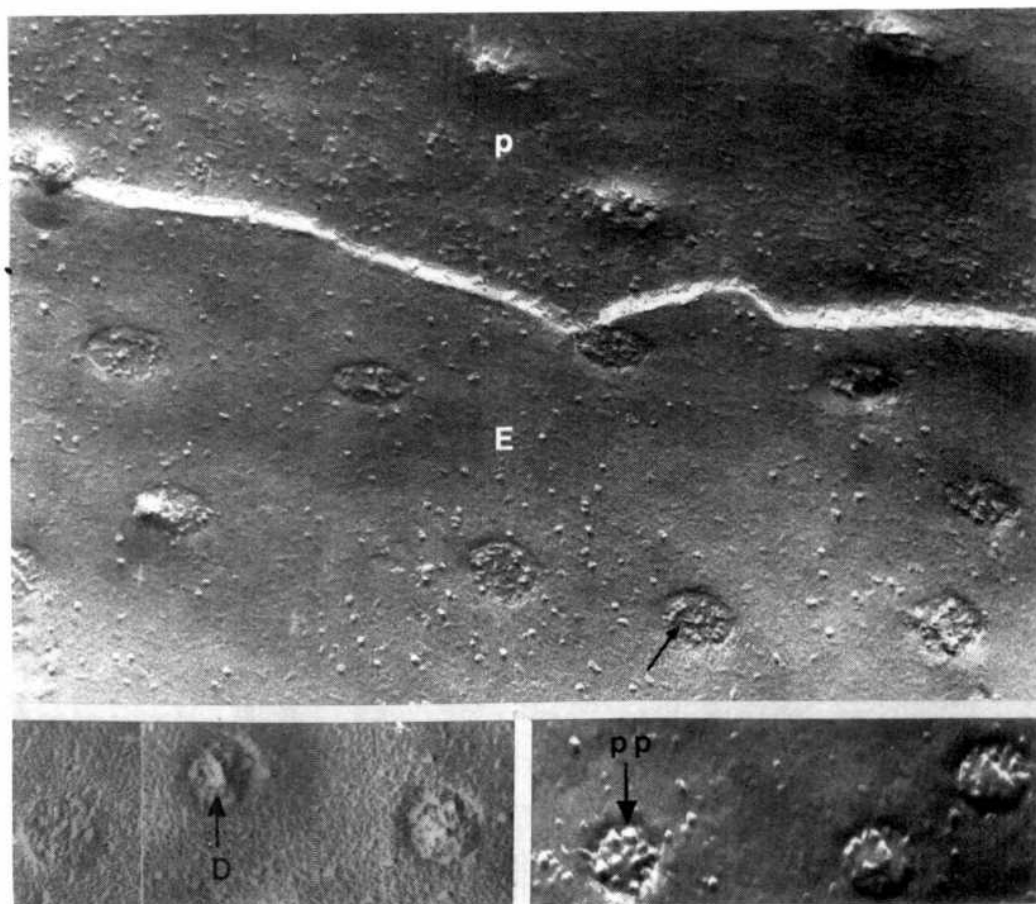


Fig. 2 Replica showing both E face (E) and P face (P) of a cleaved endothelial cell membrane. The arrow indicates possible connections between diaphragm and peripheral particles. Peripheral particles (pp) and diaphragm (D) shown below. ($\times 132\,000$).

their substructures on both fractured faces are shown (Fig. 4). For uniformity prints were enlarged to give $1\text{ mm} = 9.6\text{ nm}$. The calculated average diameter of the pores on the E face is 78.5 nm . That of the central diaphragm is 30 nm , and the size of each peripheral particle is approximately 12 nm . Thus the calculated average space between the peripheral particle and the diaphragm is about 12 nm . On the P face the average diameter of the fenestration was found to be 76.5 nm , of the diaphragm 23.7 nm , and of the peripheral particles 13.8 nm , thus leaving a space of 12.7 nm . Details are summarised in Table 1.

By means of the Markham technique,¹⁵ pores were rotated on a printing stage. Ten circular, tangentially cleaved fenestrae on the E face and seven on the P face were selected and printed in a different number of rotations ($n=3, 4, 5, 7, 8$, and

Table 1 Average size of pores and their subunits on E and P face

	Size in nm	
	E face	P face
Pore diameter	78.5	76.5
Diaphragm diameter	30.0	23.7
Size of a peripheral particle	12.3	13.8
Calculated space between diaphragm and peripheral particles	12.0	12.7

10). Enhancement of peripheral particles was maintained in all pores when they were rotated 8 times. It is therefore assumed that there is a regular structural pattern of 8 particles at the pore's rim on both E face and P face (Fig. 5).

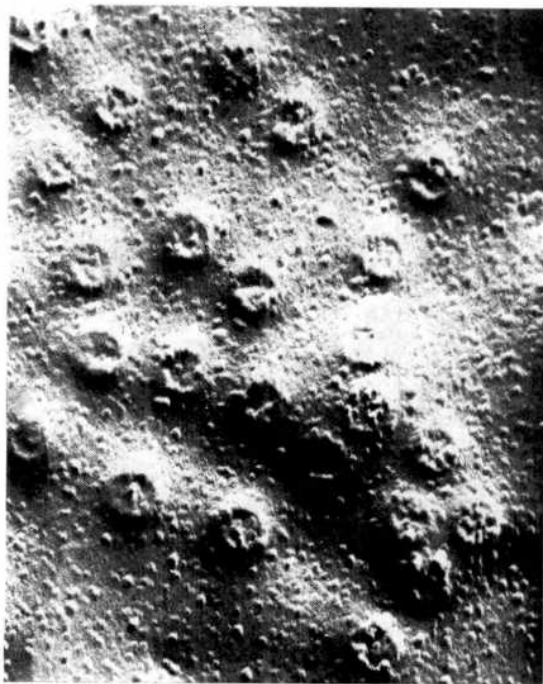


Fig. 3 P face of a cleaved endothelial cell membrane. Note the elevated particulate rim and central clusters of particles representing the diaphragm. ($\times 87\,570$).

Discussion

The ultrastructure of capillary fenestrae in the kidney, pancreas, and intestinal tract has already been described in some detail.⁷⁻¹⁰ In the choriocapillaries the existence of a diaphragm or central density was confirmed by thin sectioning and freeze-fracturing.¹⁻⁶ Spitznas *et al.*⁵ have described the diaphragm as a central thickening measuring approximately 30 nm, while fenestral diameter in their material was found to be 60 nm. Raviola⁶ has also described a central diaphragm in freeze-fractured replicas of choriocapillary fenestrations, but no measurements were carried out. Hogan *et al.*,⁸ describing thin sections of pores, found their diameter to be about 80 nm. Our study confirms the random distribution of fenestrae interrupted by cytoplasmic areas as described in the mouse renal papilla,⁷ and for the human choriocapillaries.⁵ In addition our finding of mean pore diameter is closer to that found by Hogan *et al.*⁸ We found the pore diameter to be 78.5 nm on the E face and 76.5 nm on the P face. The central diaphragm diameter was found to be about 30 nm on the E face (similar to the reported size of 30 nm by Spitznas *et al.*⁵) and 23.7 nm on the P face. The

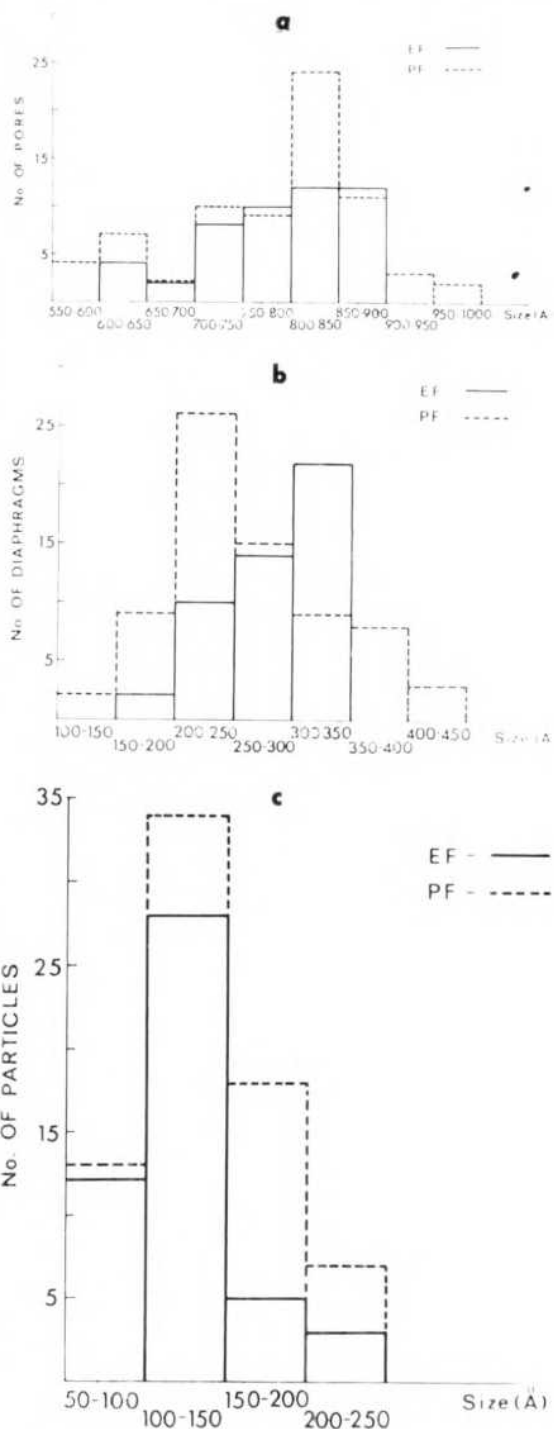


Fig. 4 Histograms showing size distributions of fenestral elements. a. Pore's diameter. b. Diameter of diaphragm. c. Size of peripheral particles.

difference between diaphragm measurement on the E face and P face is attributed mainly to difficulties in measurements, as stated above.

In our study we have postulated the existence of peripheral particles at the pore's rim. Eight regularly arranged particles were shown and their

octagonal pattern was enhanced repeatedly by the Markham method¹⁵ in different pores, implying a consistent substructure. In occasional pores fine radiating rays could be observed connecting the peripheral particles with the diaphragm. The existence of such connections raises the possibility that

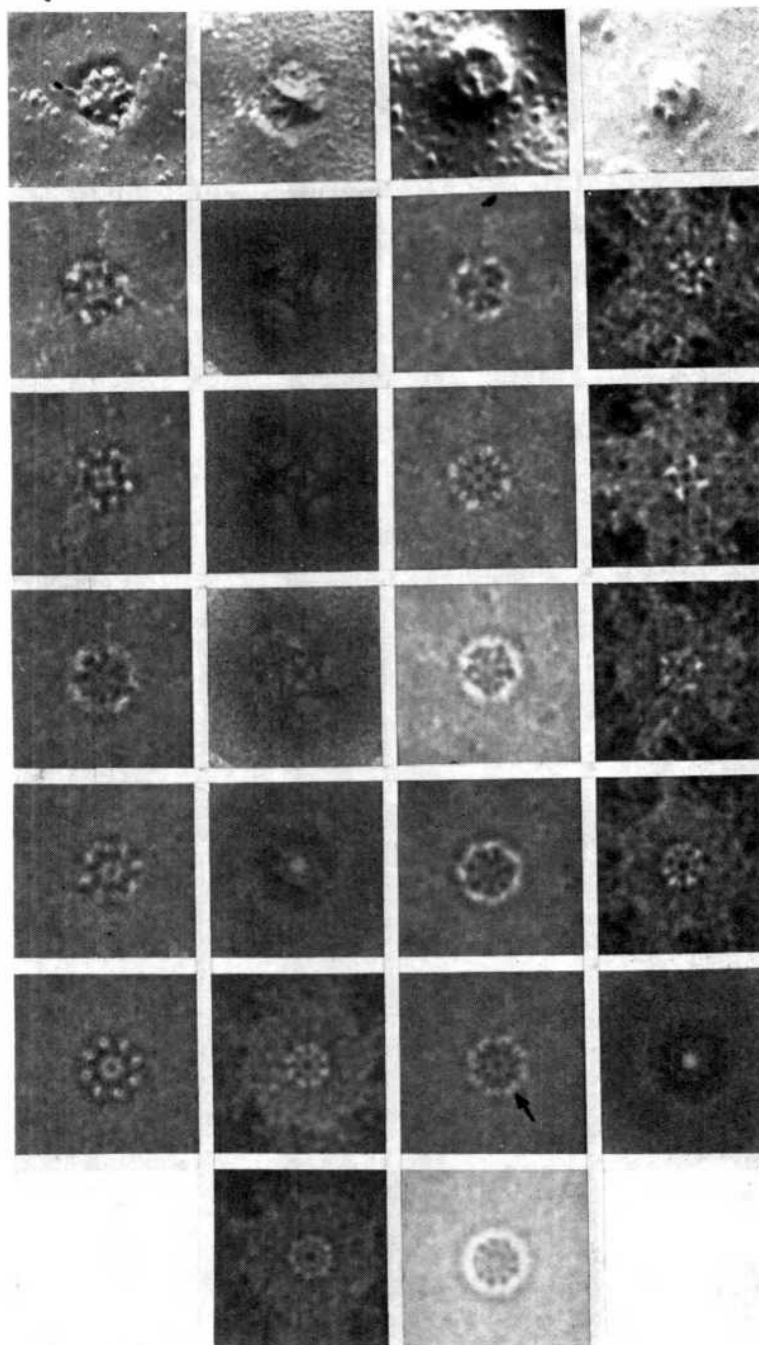


Fig. 5 Rotation of pores according to the Markham method. Top row shows the unrotated prints. The 2 on the left side are pores on the E face, the 2 on the right are on the P face. Rows 2, 3, 4, 5, 6, 7 represent rotations of $n=3, 4, 5, 7, 8$, and 10 respectively. Marked enhancement results at $n=8$ rotations. Note (arrow) that occasionally enhanced P face particles looked as if composed of 2 subunits.

Fig. 6 Schematic drawing of possible cleavage planes within the fenestrae. A. Cleavage plane splitting the Bruch's membrane orientated side. B. Cleavage plane splitting the scleral orientated side. C. Cleavage plane passing by the fenestral elements.

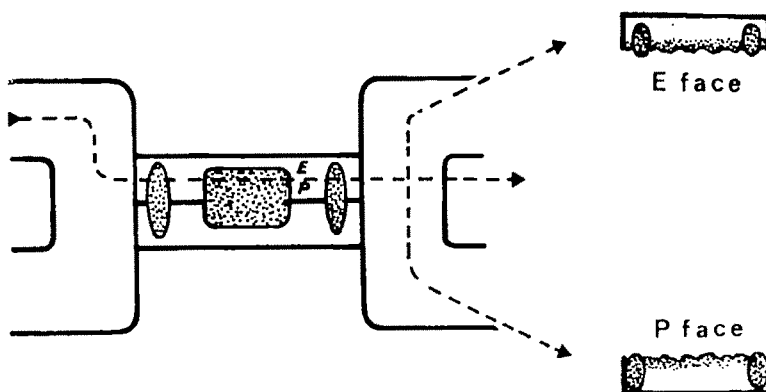
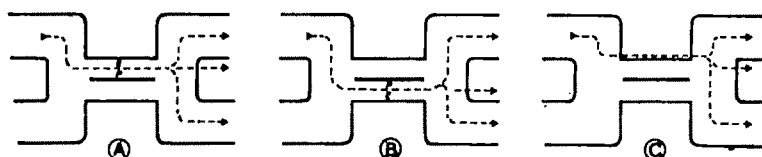


Fig. 7 Schematic presentation of possible integral proteins crossing the fused membranes which form the fenestration. Possible cleavage planes through these integral proteins are also depicted.

these intrafenestral structures may be involved in the control of macromolecular leakage by active stretching and relaxing of the diaphragm, thus changing the diameter of the passages available for macromolecular permeability from the choroid to the retina. This study was not aimed at investigating the occurrence of contractile elements associated with the peripheral particles. The possibility that the intrafenestral system acts as a sieve-like mechanism cannot be excluded and deserves a further study.

The calculated space of 12.0–12.7 nm between diaphragm and peripheral particles corresponds well with the 'small pore' theory, enabling small molecules such as peroxidase (5 nm) to pass through the pores, while larger molecules like ferritin (11 nm) cannot pass freely.¹¹ If, as suggested by Maul,¹⁰ the pore is created by fusion of the 2 adjacent membranes, one has to presume that the appearance of the fenestrae on the P face would fit with its counterpart on the E face. This is true to a limited extent. The pattern of practically all pores on the P face, when compared to each other, was found to be similar; the same applies to those observed on the E face. However, it would be expected that if the peripheral particles on one face are protruding, the other fractured face will show their imprints, namely, small shallow 'craters'. That was not the case, as protruding peripheral particles were observed on both fractured faces. A possible

explanation might be that the protruding particles observed on both faces represent 2 halves or 2 subunits of integral proteins which cross the 2 fused membranes, and that the cleavage plane passed through them rather than around them.

The possible cleavage planes within the fenestral elements are schematically depicted (Fig. 6). A possible cleavage plane sparing the diaphragm (above it or below it), thus creating a smooth face inside the pore, is also included. Several pores of that appearance were encountered. If the pore elements are considered to be formed as a result of

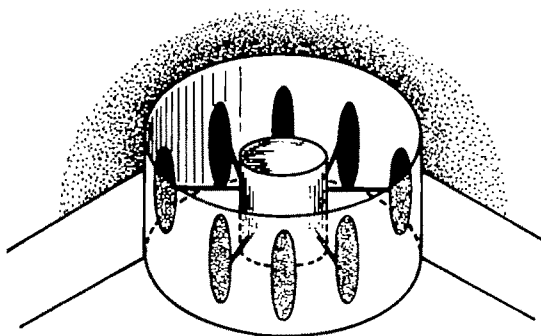


Fig. 8 A possible 3-dimensional model of a chorio-capillary endothelial fenestration. The calculated space between diaphragm and peripheral particles was found to be 12.0–12.7 nm.

adhesion or fusion of endothelial cell membranes, the P faces should be adjacent to the centre of the pore, while the E faces are external. The similarity of practically all E face pores and P face pores favours the possibility of a symmetrical arrangement at the width of the pores' element.

Fig. 7 shows schematically why the repeatedly protruding particles on both the E face and P face might be explained by the passage of the cleavage plane through the postulated integral proteins. Having described the regularity of the 8 peripheral particles with their average size and possible connections with the diaphragm, we suggest a possible 3-dimensional model of the fenestration in the choriocapillary (Fig. 8).

This study was supported by a grant from the Israeli Ministry of Health.

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Correspondence

Wooden orbital foreign body

SIR, My communication is regarding an article by Mr John A. Macrae entitled *Diagnosis and management of a wooden orbital foreign body: case report*.¹ If this case report history is presented in a chronological order, fundus examination with binocular indirect ophthalmoscopy was performed 3½ weeks after the initial injury and only after CAT scan and orbital ultrasonography were done. It appears from the drawing in Fig. 3 that indirect ophthalmoscopy gave the diagnosis, without question, of indentation of the eye from an external source, i.e., an inferior orbital foreign body. Mr Macrae goes on to stress that 'the case dramatically illustrates the limitations of both CAT scanning and ultrasonography in the diagnosis and localisation of a wooden foreign body situation in the orbit'. I am in complete agreement with that statement but am somewhat distressed that these tests were done prior to completion of an ocular examination including indirect ophthalmoscopy, which would have given the diagnosis, in my opinion.

I agree with Mr Macrae's closing statement: 'however, as Duke-Elder (1972) stressed, it should be considered potentially hazardous to embark on blind exploration for a suspected wooden foreign body without positive proof of its position or even its existence'. However, in my opinion indirect ophthalmoscopy would have given the 'positive proof' early in the patient's illness and would negate the absolute necessity of doing a CAT scan and ultrasonography.

DONALD L. HALL

2751 Virginia Avenue,
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Reference

¹Macrae JA. Diagnosis and management of a wooden orbital foreign body: case report. *Br J Ophthalmol* 1979; 63: 848-51.

SIR, May I thank Dr Hall for his letter and comments about my paper. In his letter Dr Hall expressed concern that CAT scanning and ultrasonography had apparently been performed prior to indirect ophthalmoscopy of the injured eye, and he also suggested that the fundus lesion described gave 'positive proof' of the presence and position of the retained wooden foreign body.

It was in fact stated in the presentation that funduscopy by direct ophthalmoscopy was normal at the time of the patient's admission. However, I apologise for not clarifying the fact that fundus examination was performed intermittently thereafter, with full mydriasis by both direct and indirect ophthalmoscopy. The fundus lesion

described in the paper was not present initially and only became apparent some 4 weeks later during the course of the post-traumatic inflammatory reaction. The lesion subsequently subsided and disappeared during the administration of systemic and topical steroid therapy.

The evolution of the fundus lesion was therefore characteristic of the development and resolution of a granulomatous inflammatory reaction in the traumatised area and did not provide the 'positive proof' necessary to consider further surgical exploration at that time. The 'positive proof' was provided later by the presence of a sharply circumscribed palpable mass on the subsidence of the surrounding tissue reaction. Surgical intervention prior to that clinical finding would have involved the blind exploration deprecated by Duke-Elder.¹

JOHN A. MACRAE

Ninewells Hospital and
Medical School,
Dundee DD2 1UB

Reference

¹Duke-Elder S. *System of Ophthalmology*. London: Kimpton, 1972: 14 (1): 666-7.

Notes

Microsurgery course

The Department of Clinical Ophthalmology of the Institute of Ophthalmology will be conducting a course in ophthalmic microsurgery on 8-10 October 1980. It will be a practical course concerning common intra-ocular surgical procedures. The fee is £100, and the closing date for applications is 1 September. Application forms and further details may be obtained from the Microsurgical Course Secretary, Department of Clinical Ophthalmology, Moorfields Eye Hospital, City Road, London EC1V 2PD. A further microsurgical course will be held in the spring of 1981.

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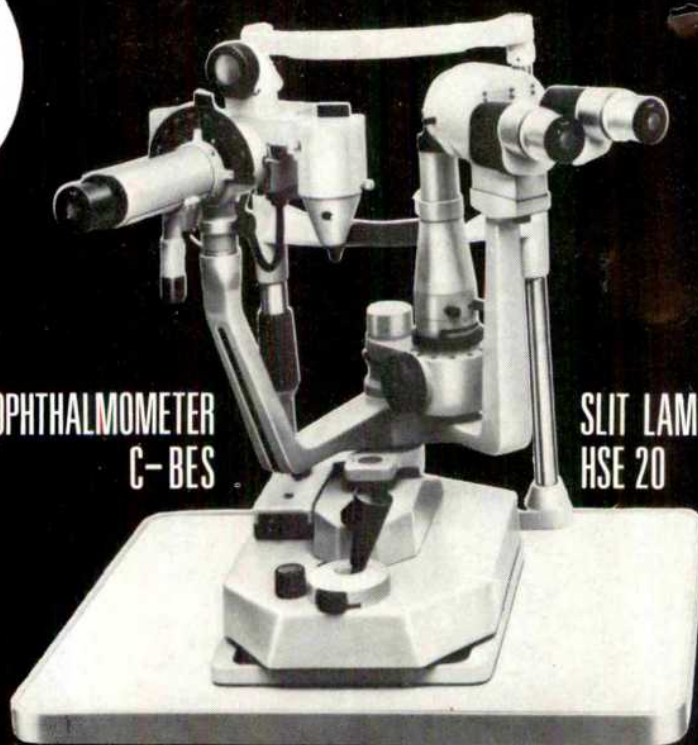
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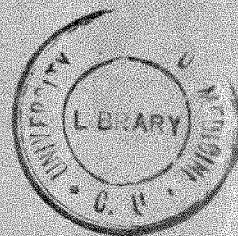
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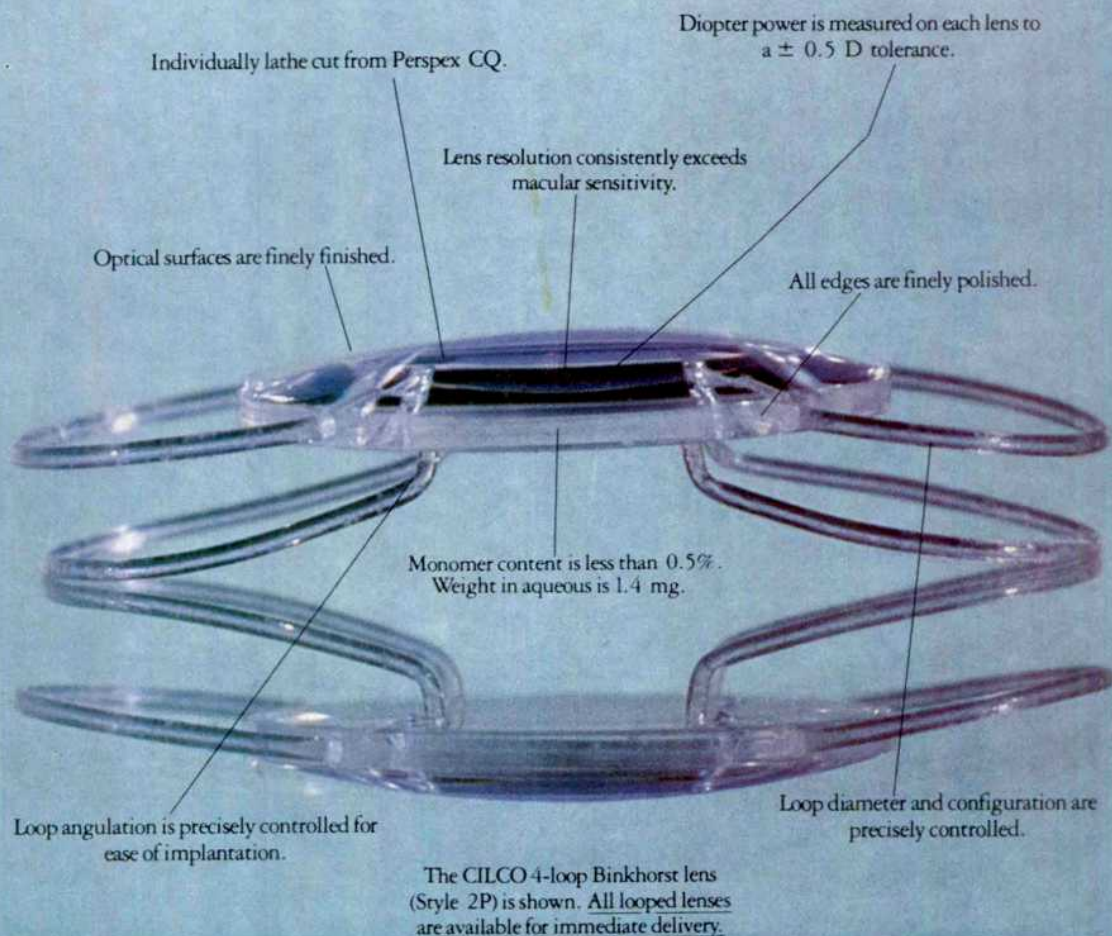
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Management of optic nerve gliomas

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SUMMARY Seventeen patients thought to have orbital optic nerve gliomas when first seen have been reviewed after up to 12 years. Enlargement of the optic canal was present in 15 of the 16 patients examined, but this finding was unreliable as an indicator of the posterior extent of the tumour. Nine patients had a stable course with little change over a period of up to 8 years; there was optic atrophy in all and neurofibromatosis was relatively common (7/9). Eight patients showed progressive enlargement of the tumour; 6 had swollen discs, and the incidence of neurofibromatosis was relatively low (3/8). The optic nerve was excised in 7 of the latter group. Biopsies of the optic nerve taken from the region of maximal enlargement were difficult to interpret and unhelpful in planning management. Radical surgery should be reserved for the minority of patients in whom there is progressively enlarging tumour without evidence of chiasmal involvement.

Gliomas of the optic nerve are relatively uncommon lesions, and their natural history and management are the subject of considerable debate. In 1969 Hoyt and Baghdassarian¹ suggested that these tumours behaved as hamartomas and concluded that the management of patients with them should be conservative. We have seen 17 patients with optic nerve glioma in the past 12 years, and it has become clear that an appreciable proportion of them have had a progressive course. As a result our attitude towards treatment has changed. In this paper we record our experience of these patients and outline our present approach to their management.

Patients and methods

The diagnosis of optic nerve glioma was made in 17 patients out of more than a thousand with orbital disease seen at the Orbital Clinic at Moorfields Eye Hospital between 1968 and 1980. The diagnosis was initially made clinically on the basis of poor vision in association with proptosis and optic atrophy or swelling of the optic disc, and radiographic evidence of enlargement of the optic foramen. In 1 patient the optic foramen was normal; 1 child was too young to co-operate for optic foramen views; and in 1 patient there was no proptosis during the period of observation. Enlargement of the optic nerve was,

however, demonstrated in these 3 patients. Further details are given in the section on 'Results'. In patients seen later in the series enlargement of the optic nerve on CT scans was required for the diagnosis. The clinical diagnosis was confirmed histologically in 7 cases.

In all patients a detailed clinical history was obtained and a full ocular and neurological examination was carried out. If the patient was old enough to co-operate, the visual fields were charted; in some patients pattern visual evoked potentials (VEP) were recorded. The neurologist, in addition to assessing the state of the central nervous system, checked for stigmata of Von Recklinghausen's neurofibromatosis, using the criteria of Crowe and Schull,² and interviewed the family to see if there was evidence of neurofibromatosis in the relatives. Radiographic examination of the patients included routine skull films together with optic canal views in each case. In many patients axial hypocyclusoidal tomograms were obtained.

Patients with a slowly progressive or static lesion (as monitored by visual acuity, field charts, and degree of proptosis) were seen at least yearly by the ophthalmologist and the neurologist. Patients with a more progressive lesion were usually seen every 4 weeks.

Initially a biopsy of the optic nerve was performed in 4 patients in whom there was evidence of recent tumour enlargement. This was done to differentiate optic nerve gliomas from optic nerve meningiomas. However, without complete excision of the optic nerve the histological interpretation of the excised

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tissue proved extremely difficult. Biopsies were not therefore performed on the later cases.

If the clinical course indicated progressive enlargement of the tumour, the patient was referred to our neurosurgical colleague so that the lesion could be approached transcranially and the whole of the optic nerve from the globe to chiasm explored. In most of these cases the optic nerve from the globe to the chiasm was excised. If the chiasm was involved, surgical resection was not performed, but a shunt was inserted if hydrocephalus was present.

Results

Seventeen patients with an orbital optic nerve glioma diagnosed by the criteria defined above were included in the study. The details of their age and sex distribution are shown in Table 1. Ten of the 17 patients had Von Recklinghausen's neurofibromatosis. In 9 of these 10 café-au-lait spots were the only stigmata of the disease. The exception was a patient who presented at 38 years of age having had poor vision in one eye since at least the age of 11; she had multiple cutaneous mollusca fibrosa.

The presenting symptoms were particularly interesting (Table 2). Fourteen patients had a proptosed eye which was noticed by parents. Eight of these 14 patients had no complaint other than proptosis; only 4 patients had complained of poor vision in the affected eye, while 2 had a convergent squint in addition to proptosis. Of the remaining 3 patients 2 were noted to have a squint and diminished vision when examined in a school clinic. One patient, the oldest in the series, had noticed a pro-

Table 1 *Orbital optic nerve glioma, clinical data*

Total patients	17	
Sex	Male 4	Female 13
Involved orbit	Right 9	Left 8
Age at presentation	Mean	20.4 years
	Median	5.5 years
	Range	2-38 years
Age at onset of symptoms	Mean	4.5 years of age
	Range	0.5-18 years of age

Table 2 *Initial complaint*

Proptosis	8
Proptosis and poor visual acuity	4
Proptosis and squint	2
Squint and poor visual acuity	2
Poor vision	1

Table 3 *Clinical presentation*

	Present	Absent
Proptosis	15	2
Poor vision	17	—
Relative afferent pupillary defect	17	—
Optic disc swelling	6	—
Optic atrophy	11	—
Enlarged optic canal	15	1
Neurofibromatosis	10	7

Table 4 *Visual acuity on presentation*

Visual acuity	Number of patients
6/18	1
6/24	4
6/36	4
C.F.	1
PL	3
NPL	4

PL=perception of light. NPL=no perception of light.

gressive deterioration in the vision of the affected eye but did not notice that the eye was very slightly proptosed.

All 17 patients had decreased visual acuity at the time of presentation (Table 3), ranging from 6/18 to no perception of light (Table 4), with a relative afferent pupillary defect on the affected side. Eleven patients had a pale atrophic optic disc; 1 of these patients had opticociliary shunt vessels. Four patients had a swollen optic disc, and 1 patient had a mass extending forwards into the globe and involving the whole of the optic disc. One patient with 6/24 vision in the affected eye had normal discs on presentation, but optic atrophy was noted shortly thereafter.

Fifteen of the 17 patients had proptosis ranging from 2 mm to 8 mm (mean 4 mm). Of the 2 patients who had no proptosis initially 1 developed it later. The other remained nonproptosed (4 years follow-up); enlargement of the optic nerve was confirmed by CT scan.

On initial x-ray examination 15 of 16 patients had an enlarged optic foramen on the affected side (Fig. 1).

One patient, who presented at age 5 with a 3-year history of squint and was seen on routine school visual examination to have poor vision in that eye (perception of light), had an enlarged optic nerve on B-scan ultrasonography but no proptosis or enlargement of the optic foramen. During the next 2 years she developed a proptosis of 3 mm, which has remained static for 12 months; radiographs of

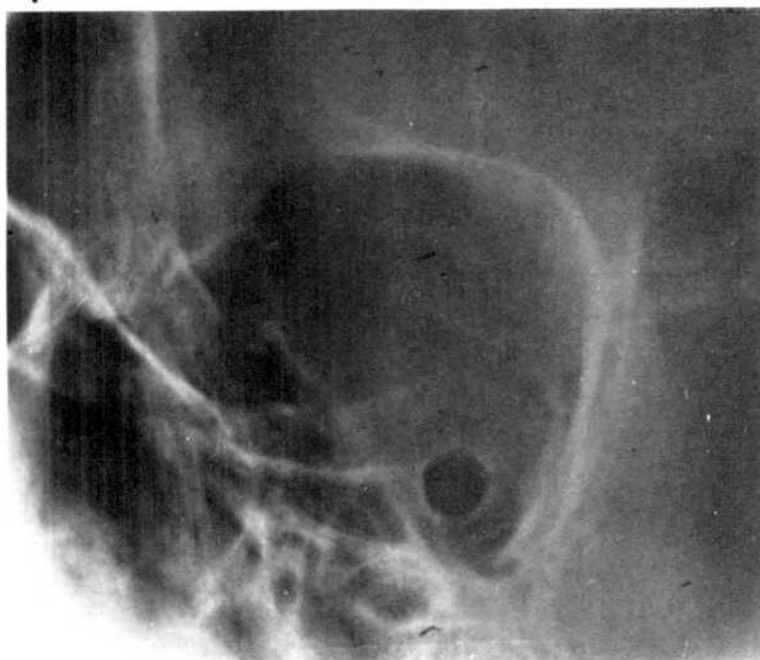


Fig. 1 Oblique radiograph of skull showing rounded enlargement of the optic canal typical of optic nerve glioma.

her optic foramen remain normal. One other patient was too young to co-operate for optic foramen x-ray views but had an optic nerve glioma verified histologically. CT scans always showed the position of the mass, but it was impossible to differentiate between the tumour and any adjacent arachnoid hyperplasia. In several cases thickening of the contralateral clinically normal nerve could be seen (Fig. 2).

CLINICAL COURSE

The clinical course of the patients was variable. Nine patients had a slow indolent course during several years' follow-up (mean 4.2 years, range 1–8 years). Three of these patients were eventually lost to follow-up, but in each case there had been no significant change in the symptomatology prior to the child and parents defaulting. All but 3 patients had symptoms for longer than 1 year before presentation (mean 2.5 years, range 4 months–9 years). The mean age at presentation of this group was 6.1 years (range 2–15 years). Vision when first seen ranged from 6/18 to no perception of light. All patients but 1 had proptosis. In all cases the optic nerve head was atrophic and flat, with shunt vessels present in 1 case. Seven of the 9 patients had neurofibromatosis.

Thus the patients in the above group showed little change in the level of visual acuity and field of vision. Two patients improved. In 1 child the

vision in the affected eye improved slightly with patching, and in another case the proptosis resolved during a 3-year period.

Eight patients showed evidence of growth of the tumour and 7 had the affected nerve excised. The mean age of presentation of this group was 5.8 years (range 2.5–20 years), with a relatively brief duration of symptoms (mean 1.6 years—range 2 months to 8.5 years). Vision on presentation was poor, ranging from 6/24 to no perception of light. The optic disc in 6 patients was swollen; in another 2 the disc was atrophic. One of these patients had shunt vessels on the disc. Three patients had neurofibromatosis. The individual clinical details of patients in this group are worth recording.

CASE REPORTS

Patient 1. A 3½-year-old girl with neurofibromatosis developed a progressive left proptosis for 4 months before attending the Orbital Clinic. The left eye was blind and proptosed 4 mm. The optic disc was swollen and invaded by a cream coloured mass which extended forwards into the vitreous. Radiographs showed an enlarged left optic foramen, and B-scan ultrasound showed a solid retrobulbar mass with extension into the optic nerve head. Because of progressive proptosis the optic nerve was explored through a medial conjunctival incision 1 year after the child first attended the clinic. Incision of the dura released a large quantity of mucinous material,

The biopsy showed an intact dural sheath with an underlying area of meningeal hyperplasia. CT scans showed enlargement of the whole of the optic nerve from the globe to the chiasm. The child was referred to our neurosurgical colleague and the affected optic nerve removed from behind the globe to the chiasm, which was not involved, through a frontal craniotomy. Histologically the tumour was a grade 1 astrocytoma. No tumour was present at the cut surface of the intracranial portion of the nerve. Intractable glaucoma developed, and the globe was enucleated 5 months later. Nine months after the craniotomy the child's prosthesis became displaced by an enlarging orbital mass; biopsy of this lesion showed recurrence of the glioma. The mass continued to enlarge and the orbit was eventually partially exenterated. She is alive with no sign of a recurrence of the tumour 2 years after her last operation.

Patient 2. An 8-year-old girl with a 4-month history of progressive left proptosis was referred to this clinic. The affected eye was proptosed 3 mm and convergent 40°. Vision was reduced to 6/36, the left optic disc appeared hypoplastic, with swelling of the nerve head in the upper nasal quadrant. There were no stigmata of neurofibromatosis. Radiographs showed enlargement of the left optic canal. The pattern VEP showed a normal response from the right eye. The optic nerve was explored through a medial transconjunctival approach; incision of the dural sheath released mucinous material. A portion of the sheath together with the underlying tissue was excised and was reported as showing meningotheelial cells, fibrous tissue, and a few well differentiated glial cells. During the next 3 years the visual acuity in the left eye further decreased to 6/60. The proptosis increased to 10 mm. CT scans showed an ill-defined expansion of the left optic nerve, but the intracranial scan was normal, as was an air encephalogram. The intracranial and intracanalicular portion of the optic nerve were removed through a frontal craniotomy. Histopathological examination showed a normal optic nerve with an extensive collar of meningotheelial cells and intermingled psammoma bodies. No evidence of glial hyperplasia or astrocytic glioma was seen throughout the intracanalicular or intracranial portions of the optic nerve. She was diagnosed as having a primary optic nerve meningioma. Three months later a large tumour mass continuous with the optic nerve was excised through an anterior orbitotomy, and the optic nerve was divided flush with the globe. Histological examination showed a typical grade 1 astrocytic glioma of the optic nerve with extensive meningotheelial cell proliferation and numerous psammoma bodies. The child is alive and well with

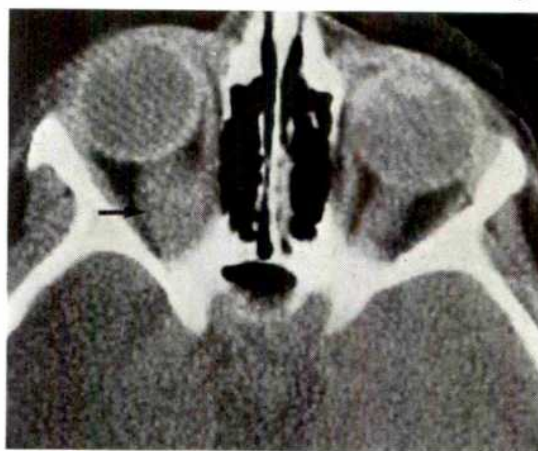


Fig. 2 Axial CT scan showing left optic nerve glioma (arrowed). The right optic nerve is diffusely enlarged; the right visual field and acuity were normal.

no sign of a recurrence after 2 years.

Patient 3. A girl presented at the age of 5½ years with a 4-month history of a left divergent squint and a 2-month history of proptosis. Her blind left eye was proptosed 3 mm, divergent 25°, and the optic disc was swollen. The right eye was normal in all respects with an unaided vision of 6/6; the VEP was normal from this side. There were no signs of neurofibromatosis. Radiographs showed an enlarged left optic foramen. Eight months later the divergent squint was surgically corrected and the optic nerve explored. A biopsy of the nerve showed hyperplastic meningeal tissue. Four months later the VEP showed evidence of involvement of the nasal fibres from the right eye, though a field defect could not be detected by perimetry. Twelve months later she experienced severe left hemicranial headaches with nausea and vomiting, which after several months subsided spontaneously. Three years after her initial presentation perimetry showed a right superior temporal quadrant field defect. By this time the left eye was proptosed 9 mm. CT scans showed a large left optic nerve mass with involvement of the chiasm. An air encephalogram showed a moderate degree of symmetrical hydrocephalus, with the third ventricle displaced upwards and almost obliterated by a large suprasellar mass. A left frontal craniotomy was performed, during which it was found that the tumour involved both optic nerves together with the chiasm. Posteriorly the tumour surrounded the left internal carotid and anterior cerebral arteries. Portions of the tumour were removed for histological examination. Examination showed the tumour to have the features of a grade 1 astrocytoma. 5500 rads of radiotherapy

were given to the chiasm and the left orbit. Subsequently the shunt for hydrocephalus was removed. She remains alive and well without progression of the proptosis or visual field deficit for the past 4 years.

Patient 4. A girl was seen at the age of 2½ years with a 2-month history of proptosis and poor vision in the left eye. Vision in the affected eye was reduced to 6/36; the eye was proptosed 3 mm, and the optic disc was swollen. No signs of neurofibromatosis were seen. X-rays showed an enlarged left optic foramen and CT scans enlargement of the intra-orbital part of the left optic nerve. A biopsy of the optic nerve through a medial conjunctival approach was performed and was reported as showing astrocytic proliferation with occasional Rosenthal fibres. It was not possible to tell whether the biopsy was of the nerve itself or of an extension of tumour tissue into the sheath; meningotheial cells were not present. During the ensuing 6 months the proptosis increased 6 mm, and the child was transferred to the care of our neurosurgical colleague. An air encephalogram showed no evidence of intracranial extension. The whole of the optic nerve from the globe to the chiasm was removed through a transfrontal craniotomy. Histologically the tumour was an astrocytoma grade 1. At operation it was thought that the tumour did not involve the chiasm, but microscopically the cut end of the intracranial portion of the nerve showed gliomatous tissue. Apart from postoperative ptosis the child is well 6 months later.

Patient 5. A girl aged 7½ years was brought to the clinic having noticed poor vision and progressive protrusion of the left eye for the previous 2 months. Her left eye was proptosed 4 mm, the vision was reduced to 6/36, and the optic disc was swollen. Radiographs showed enlargement of the left optic canal and CT scans enlargement of the optic nerve to the orbital apex. VEPs were obtained from the right eye and were reported as being within normal limits. The patient was referred to our neurosurgical colleague for removal of the optic nerve because of the rapidity of the growth of the tumour. The nerve was totally excised, but there was histological evidence of glioma at the cut end of the intracranial part of the optic nerve. Histologically the tumour was a grade 1 astrocytoma. The child is well with no signs of a recurrence of the tumour 9 months after surgery.

Patient 6. The father of a 6-year-old girl had noticed that his daughter's left eye had become progressively prominent for 6 months prior to consulting an ophthalmologist. The eye was blind and proptosed 8 mm. Ocular movements were full. However, the left optic disc was swollen, with

associated peripapillary haemorrhages and exudates. A VEP from the right eye and the visual fields were normal. The child was referred to our neurosurgical colleague, who explored the chiasm but found that the glioma extended into the chiasm. Surgery was confined to obtaining a biopsy, which confirmed the diagnosis of glioma, astrocytoma grade 1. During the ensuing 15 months the amount of proptosis has increased slightly, and it is probable that a portion of the orbital part of the glioma will have to be resected in order to preserve the globe.

Patient 7. A 9-year-old girl was referred to an ophthalmologist. Her parents had noticed a slight right divergent squint since she was 6 months old. At a routine school examination it was found that the vision in her right eye was poor. At her initial examination the right visual acuity was 6/24, with an associated slight right divergent squint. She was initially treated with partial occlusion of the left eye, but after 18 months it was noticed that the vision in her right eye had deteriorated, and she could only count fingers in the upper half of the visual field. At the same time she was found to have a pale right optic disc, and the eye was proptosed 3 mm. She was subsequently referred to the Orbital Clinic, where x-rays of her skull showed enlargement of the right optic canal. There was no evidence of neurofibromatosis. During the next 5 years vision in her right eye deteriorated to the appreciation of hand movements at 0.25 metre and the proptosis increased to 6 mm. The visual field in the left eye was examined at regular intervals and the VEPs were obtained. Four years after her initial presentation the VEP showed evidence of a temporal field defect. Twelve months later there was definite evidence of a central temporal half field defect in the right eye by conventional perimetry. CT scans showed enlargement of the right optic nerve with evidence of chiasmal involvement. The child was transferred to Maida Vale Hospital for a pneumo-encephalogram, which revealed a suprasellar mass and hydrocephalus. The patient died after the procedure. Permission for a necropsy was declined.

Patient 8. A 20-year-old female student had noticed blurring of right vision for 18 months with prominence of the eye for 12 months before consulting an ophthalmic surgeon. During the ensuing year vision in the affected eye deteriorated, and the degree of proptosis increased. A neurosurgeon from another centre performed a transfrontal approach to the right orbit but was unable to find any abnormality. After an ineffective 6-week course of systemic steroids the patient was referred to this hospital. Her right eye was proptosed 5 mm and displaced downwards 3 mm; upward movement of the globe was selectively restricted. The optic disc was pale

and flat, though a year previously definite swelling had been noted. There were numerous opticociliary shunt vessels. A CT scan showed gross enlargement of the optic nerve immediately behind the globe. Subsequently the orbital portion of the optic nerve containing a large grade 1 astrocytoma was excised through a lateral orbitotomy approach. During a 4-year follow-up there has been no recurrence of the tumour.

Discussion

The outstanding finding of the present investigation is that our patients fell into 2 fairly distinct groups with differing clinical course. Nine patients had an indolent course with little change in the size and extent of the tumour. In the remaining 8 patients the tumours progressively enlarged.

The age distribution of the patients at presentation was similar in the 2 groups, but the progressive group had a shorter history and a relatively rapid increase in proptosis during the period before and soon after the initial consultation. Other evidence of rapid tumour enlargement was found in the ocular fundus. In 6 patients the optic disc was swollen when the patient was first seen. This was in contrast to the more stable group of patients in whom none had evidence of optic disc swelling, though there was optic atrophy in all cases. Of particular interest was patient 7, in whom there was evidence of a quiescent glioma for 9 years before the eye became proptosed. Five years later she had developed a field defect in the contralateral eye and the proptosis had increased considerably. This case was exceptional, but it does illustrate that enlargement of a glioma of the optic nerve can occur in patients who have been clinically quiescent for some years.

There was a significant difference in the incidence of neurofibromatosis in the 2 groups. The overall incidence was rather higher (10/17, 63%) than in previous reports,¹⁻⁸ as low as 10%⁶ and as high as 50%.⁸ Only 3 of 8 patients in the progressive group had neurofibromatosis compared with 7 out of 9 with quiescent tumours. This observation accords with the views of Martin and Cushing⁹ and Lloyd⁸ and Klug,¹⁰ who reported that patients with optic nerve glioma in association with neurofibromatosis had a more benign course than patients without this association. The explanation for the wide divergence in figures for the overall incidence of neurofibromatosis is uncertain, but 3 factors are likely to contribute: (1) the relatively small number of patients in most series; (2) the difficulty of recognising the minimal clinical signs of neurofibromatosis; and (3) the delay in the development of the

stigmata of the disease in some children.

The recognition that there exist 2 groups of patients with orbital optic nerve glioma has important implications for management. Many surgeons have adopted a conservative policy following Hoyt and Baghdassarian's conclusion that gliomas of the optic pathways are indolent and slow growing and that for practical purposes they can be regarded as hamartomas, most of them requiring no active intervention. This view has been supported by a number of authors subsequently.¹¹⁻¹⁴ There is however good neuropathological evidence that at least some optic nerve gliomas are true tumours with a potential for local invasion.¹⁵ This observation, together with our experience that nearly half our patients showed clear evidence of progression, has led us to the conclusion that the potential for enlargement of optic nerve glioma in childhood is not infrequently realised, and that radical surgery should be considered for patients in which it is.

It is clear that if the chiasm is already involved when the patient presents a radical cure is not possible. In these circumstances surgery should be confined to the treatment of complications such as disfiguring proptosis or hydrocephalus, as Hoyt and Baghdassarian suggest.¹ The first step in the assessment of the patient must therefore be to try to determine whether or not the tumour is confined to the orbit. We have used 3 approaches to this problem.

(1) *Radiological examination of the optic canals.* There was evidence of enlargement in 15 out of 16 of our patients. In several of these patients, however, surgical exploration showed that the glioma did not extend into the enlarged canal. As others have noted,¹² the widened canal could be associated with dural thickening or arachnoid hyperplasia. The size of the optic canal thus gives little indication of the posterior extent of an optic nerve glioma.

(2) *CT scanning.* The advent of high resolution CT scanning in both axial and coronal planes has enabled tumours arising from the optic nerves to be recognised much more readily than was possible previously. Again, however, it is not possible to distinguish between gliomatous tissue and meningeal hyperplasia. Moreover, enlargement of the chiasm by tumour may still be difficult to detect even with the very high resolution scanners now available. Pneumoencephalography is more reliable, but as Anderson and Spencer¹⁶ have reported, and our cases 4 and 5 confirm, the absence of macroscopic enlargement of the chiasm does not exclude involvement by tumour.

(3) *Visual field examination.* The most sensitive methods for detecting involvement of the nerve fibres from the other eye are perimetry and VEP

examination. Halliday *et al.*¹⁷ have shown that it is possible to detect abnormalities in the pattern VEP before a field defect is demonstrable clinically. In 2 of our patients (patients 6 and 7) there was electrophysiological evidence of a temporal field defect 6 and 12 months before it could be demonstrated by conventional perimetry. However, even this sensitive technique failed to show chiasmal involvement in 2 of the cases (4 and 5), in whom the face of the optic nerve severed at its junction with the chiasm showed histological evidence of tumour. These observations indicate that abnormal tissue may be present in the visual pathways without the clinician being aware of its true extent.

Having demonstrated the presence of an optic nerve tumour and obtained some idea of its extent, the ophthalmologist must then decide whether it is appropriate to biopsy the tumour in order to establish the diagnosis. Our initial policy was not to biopsy small, apparently indolent lesions. However, when there was evidence of recent tumour enlargement and there was severe visual impairment, we obtained tissue from the nerve in the region of maximal swelling in an attempt to distinguish between optic nerve meningioma, which has a reputation in children for aggressive growth and local invasion¹⁸ and therefore requires early radical excision, and glioma. In the event, as others have found,⁸ it was difficult to interpret the biopsy findings. In 4 of the 5 biopsies there was arachnoid hyperplasia compatible with either glioma or primary optic nerve meningioma. In the fifth biopsy it was impossible to tell whether the tissue came from the nerve itself or from an extension of the tumour into the sheath. Because we have not found biopsy helpful in planning management we have abandoned it as a routine, and we restrict surgical intervention to total excision of tumours showing evidence of progressive enlargement or to the symptomatic relief of complications.

Finally there is the question of surgical approach to the expanding tumour. In our own material, as in that of others, enlargement was produced by meningeal hyperplasia and the production of mucoid material containing tumour astrocytes as well as by glial proliferation. Since it is impossible clinically or radiologically to distinguish the contribution of each to any particular tumour, we have managed all patients in the same way. If there is no evidence of chiasmal involvement, the patient is referred to our neurosurgical colleague, who explores the chiasm through a frontal approach. If inspection confirms the absence of chiasmal swelling, the affected optic nerve is sectioned at its junction with the chiasm. The optic canal is unroofed and the nerve excised to the posterior surface of the

globe. A number of authors have stated that partial removal of these lesions is all that is needed and that the chances of enlargement of the residual tumour are extremely low.^{1,19} The importance of complete excision of the nerve, however, is emphasised by the course of case 1, in which a partial removal was followed by rapid expansion of the orbital stump.

It is inevitable that in some patients tumour will be present at the chiasm despite the absence of swelling or of preoperative evidence of damage to fibres from the other eye. This was the case in 2 patients (4 and 5) of our 4 patients in the progressive group (cases 1, 2, 4, and 5), who are known to have had no macroscopic evidence of enlargement of the chiasm. The state of the chiasm in case 8 is not known. Anderson and Spencer¹⁰ have suggested that in such patients, as in those with preoperative evidence of chiasmal enlargement, the abnormal tissue may be present in the chiasm from the start, rather than having extended there from a primary orbital tumour. Our observations shed no light on this suggestion. However, given that there is unequivocal clinical and radiological evidence of tumour enlargement in some patients, it is reasonable to suppose that the chiasm might become secondarily involved by tumour tissue extending along the nerve in the same way that tumours of similar histological type, such as the cerebellar astrocytomas of childhood, extend in white matter elsewhere in the central nervous system.¹⁵ Cases 1 and 2 of the 4 patients in whom there was no macroscopic evidence of chiasmal involvement had no tumour tissue at the cut surface of the intracranial optic nerve. In these 2 patients total excision of the tumour will have removed the possibility of further involvement of the visual pathways from the orbit. They are being closely followed up to determine whether tumour subsequently develops in the chiasm. If it does, the case for an attempt at radical surgical cure will be greatly weakened.

The correct management of the child with optic nerve glioma remains a difficult problem. Our experience of the past 12 years has led us to move from a conservative to a more radical position, though as a result of our present review we think it likely that only a minority of patients should have surgery. We now believe that parents should be told that their child has a tumour of the optic nerve and that the appropriate method of treatment will be determined by the progress of the condition. In about half the patients there will be no deterioration, and management will be conservative. In the remainder progressive deterioration will suggest that the tumour is extending, and for these patients we will advise radical surgery provided there is no radiological, clinical, or VEP evidence of chiasmal

involvement. When the chiasm is involved, we will advise against surgery unless orbital or intracranial complications develop, which should then be managed on their merits.

We are grateful to Professor Lindsay Symon, who performed the craniotomies on patients 1-6; to Dr Glyn Lloyd, who performed the radiological examinations; to Dr Martin Halliday, who performed the VEP studies; and to Professor Alec Garner, Professor Leo Duchon, and Dr Robin Barnard, who carried out the histological examinations of the tumours.

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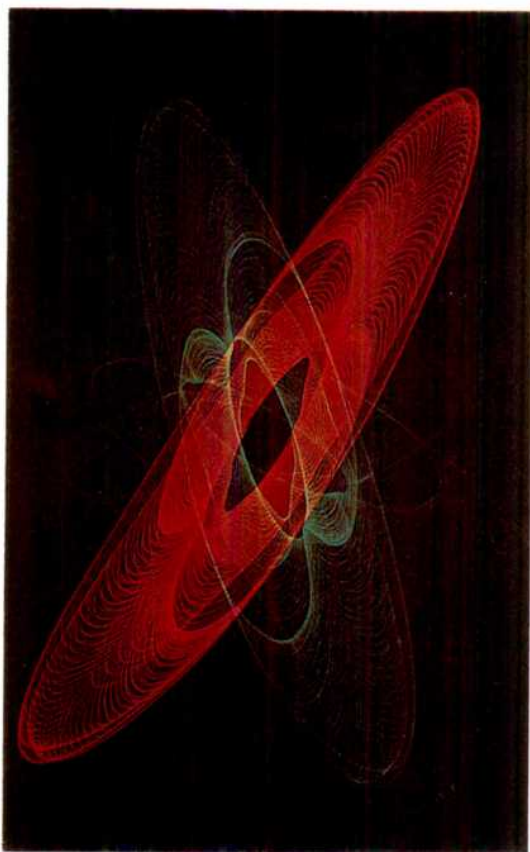
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Primary optic nerve meningioma

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SUMMARY Twenty-seven patients with a meningioma arising from within the optic nerve sheath have been seen during the past 12 years. Twenty-one were women, the majority aged 39-64 years. The men were younger, all except 1 being between 20 and 41 years when first seen. There were no patients younger than 20 years. Twenty-two patients had noticed a deterioration in the vision as their initial symptom. The optic nerve head was abnormal in all patients; 14 were swollen and 13 atrophic and flat. Neurofibromatosis was not associated with this condition. Treatment was essentially surgical.

Primary orbital optic nerve meningiomas arise from the cap cells of the arachnoid round the intra-orbital portion of the optic nerve. More rarely meningiomatous tissue may extend from adjacent structures into the orbit in the subdural space of the optic nerve (Figs. 1 and 2), a secondary optic nerve meningioma. The true origin of any meningiomatous tissue found in relation to the optic nerve must therefore be defined accurately.

Failure to do this has caused some confusion about the symptomatology and incidence of the various types of meningioma affecting the orbit. This communication analyses the mode of presentation of a series of patients with a proved primary optic nerve meningioma, correlating the signs and symptoms with the findings at surgery.

Patients and methods

Twenty-seven patients with a primary optic nerve meningioma were seen in the Orbital Clinic at Moorfields Eye Hospital since 1968. A detailed clinical history was obtained in all cases and a thorough ophthalmic and neurological examination carried out, including a search for signs of neurofibromatosis. Oblique radiographs and axial hypocycloidal tomograms of the optic canals were obtained in all patients. Since 1964 patients have been CT scanned in the axial plane; recently coronal scans have been taken. These radiographic investigations were supplemented in some cases by b and c mode ultrasonic examination of the optic nerve and orbital contents. Fluorescein angiograms were

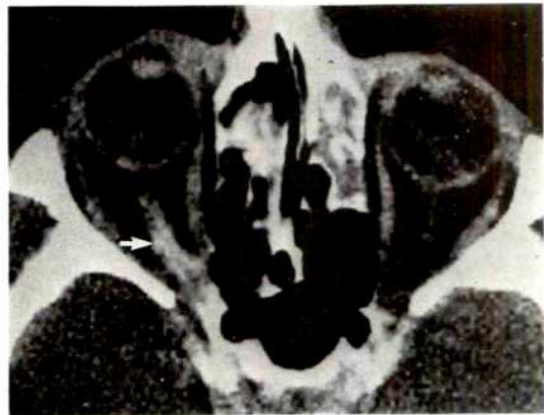


Fig. 1 Axial CT scan showing enlarged optic nerve (arrowed) caused by secondary meningioma.

performed on selected patients to define the state of the optic disc.

All patients included in this series were micro-surgically explored by lateral orbitotomy.¹ In most patients the meningioma was totally removed, leaving the optic nerve intact. Latterly the optic nerve has also been excised from the globe to the optic foramen. Patients with useful vision had biopsies taken and were decompressed by incising the dural sheath. Later, when vision failed, the lesion was excised totally.

Patients have been reviewed at 6-monthly or yearly intervals. Axial hypocycloidal tomography and CT scans have been performed on selected patients.

Results

Some of the clinical details of the 27 patients studied are presented in Table 1. Twenty-one patients were women. Twenty of these were aged

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Fig. 2 Radiograph from the same patient shown in Fig. 1, with sclerotic changes on the planum sphenoidale (arrowed).

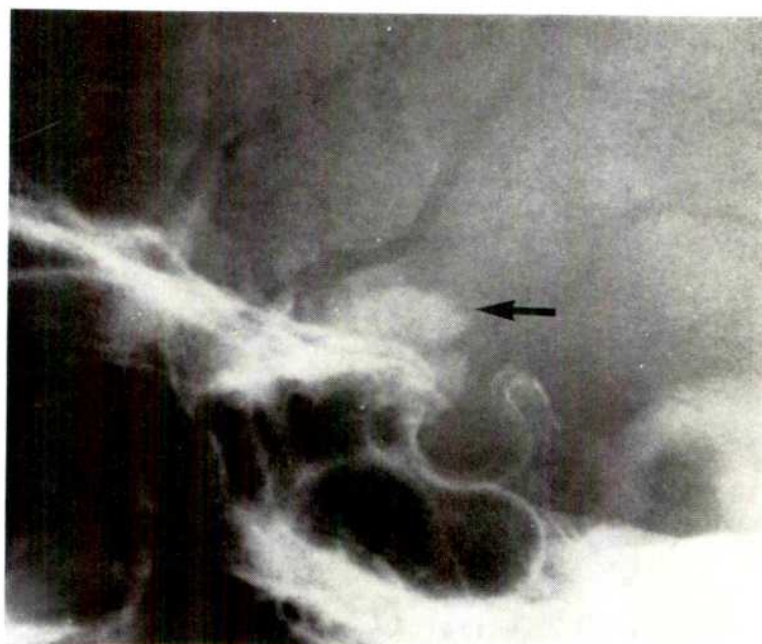


Table 1 Clinical details of 27 patients

Patient no.	Age (yr)	Sex	Side	Initial symptoms	Proptosis		Optic disc	Visual acuity
					Degree	Duration		
1	50	F	L	Visual loss, 18 mo	None	None	Swollen	Counts fingers
2	31	M	L	Visual loss, 7 yr	11 mm	6 yr	Swollen	Light perception
3	49	F	L	Visual loss, 5 yr	7 mm	8 mo	Atrophy	Counts fingers
4	64	F	R	Lid swelling, 1 yr	7 mm	1 yr	Atrophy	Counts fingers
5	43	F	R	Visual loss, 1 yr	6 mm	6 mo	Swollen	6/36
6	61	F	R	Visual loss, 3 yr	4 mm	2 mo	Atrophy	Counts fingers
7	49	F	R	Visual loss, 18 mo	2 mm	Not noticed	Swollen	6/18
8	50	F	L	Visual loss, 3 yr	2 mm	Not noticed	Atrophy	Hand movements
9	47	F	R	Diplopia, 1 yr	3 mm	9 mo	Swollen	6/9
10	28	F	R	Visual loss, 6 mo	4 mm	3 mo	Swollen	Light perception
11	41	M	L	Visual loss, 1 yr	2 mm	Not noticed	Swollen	6/60
12	39	F	L	Visual loss, 4 yr	5 mm	1 yr	Atrophy	Light perception
13	63	F	L	Visual loss, 1 yr	2 mm	Not noticed	Swollen	Light perception
14	37	M	R	Intermittent visual loss, 6 mo	None	—	Swollen	6/6
15	46	F	L	Proptosis, 6 mo	3 mm	6 mo	Swollen	Hand movements
16	48	F	L	Visual loss, 2 yr	3 mm	Not noticed	Atrophy	Counts fingers
17	48	F	L	Visual loss, 4 mo	2 mm	Not noticed	Atrophy	6/60
18	40	F	L	Visual loss, 6 yr	5 mm	3 yr	Atrophy	Hand movements
19	52	F	R	Visual loss, 4 yr	3 mm	Not noticed	Atrophy	No perception of light
20	40	F	L	Proptosis, 18 mo	4 mm	18 mo	Atrophy	6/9
21	62	M	L	Diplopia, 3 yr	2 mm	Not noticed	Atrophy	6/9
22	45	F	L	Intermittent visual loss, 5 yr	5 mm	2 yr	Swollen	6/12
23	63	F	R	Visual loss, 12 yr	3 mm	8 yr	Swollen	Counts fingers
24	54	F	L	Visual loss, 3 mo	2 mm	Not noticed	Swollen	6/60
25	40	F	L	Visual loss, 3 mo	3 mm	Not noticed	Atrophy	Hand movements
26	20	M	R	Visual loss, 6 mo	2 mm	Not noticed	Swollen	6/18
27	20	M	R	Visual loss, 3 yr	6 mm	2 yr	Atrophy	6/18

between 39 and 63 years. The exception was a 28-year-old woman who developed a rapidly progressive proptosis during pregnancy (case 10). The 6 men were younger; 5 were between 20 and 42 years; the oldest patient was 62 years old. No systemic abnormalities were found in any of these patients. Specifically no patient had signs of neurofibromatosis.

Twenty-two patients experienced a deterioration in vision of the affected eye as their initial symptom. In 20 deterioration was progressive and inexorable. Two patients experienced intermittent visual loss. One, a van driver (patient 14), noticed that his vision failed when the eye was abducted; vision returned to normal within a few minutes of his eyes assuming the straight ahead position. Five patients initially experienced no visual deterioration. Three noticed proptosis followed after an interval by visual loss. Two patients experienced double vision; one developed proptosis within 3 months, and the other had double vision for 2 years before her vision deteriorated.

Most of the patients had very poor vision in the affected eye. However 8 patients had 6/24 vision or better when they were first seen. Within 18 months their vision had deteriorated to worse than 6/60.

Twenty-five patients had a relative proptosis of 2 mm or more, with a range of 2 mm–11 mm (mean 4 mm). There was some degree of restriction of movement of the eye in 19 patients, with upward movement particularly affected in 12 patients.

The optic disc was abnormal in all patients. Fourteen were swollen, 13 were atrophic and flat. Opticociliary shunts were present in 9 patients.

Radiographs of the bones surrounding the orbit were normal in all except 2 patients, who had slight enlargement of the anterior end of the optic canal shown by axial hypocyloid tomograms. CT scans accurately delineated the extent of the optic nerve enlargement and defined the abnormal optic nerve in the coronal view (Fig. 3).

The lateral orbitotomy approach gave an excellent exposure of the optic nerve from the globe to the optic foramen. Six patients with retained central vision were decompressed by incising and removing a portion of dura overlying the tumour. The visual deterioration progressed in all patients, and useful vision was lost within 18 months. One patient with poor vision was explored and a large quantity of cerebrospinal fluid (CSF) was released once the dura was incised. No orbital tumour was found, and the lesion was thought to be an arachnoid cyst. Subsequently the proptosis increased. CT scans showed a mass in the apex of the orbit, which was a meningioma. All these patients were re-explored and the meningioma excised. Case 20 was

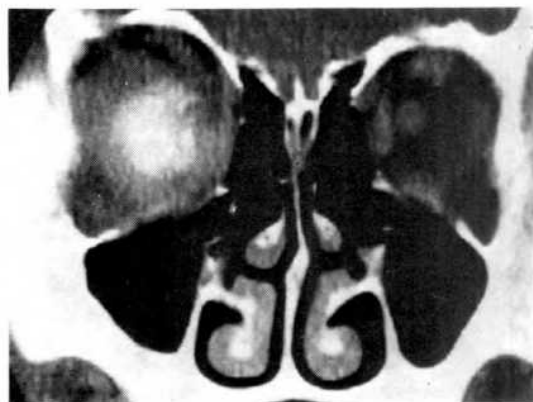


Fig. 3 Coronal CT scan showing a large optic nerve meningioma with central calcification.

an exception. Fifteen months after decompressive surgery the tumour had infiltrated the structures of the posterior third of the orbit, so that local excision with preservation of the globe was impossible. The patient awaits exenteration.

The meningioma with or without the optic nerve was excised as the primary procedure in 18 patients with poor vision when first seen.

There has been one recurrence (patient 10). A large angioblastic meningioma was removed, leaving the optic nerve intact. Six years later the proptosis recurred. A diffuse meningioma filled the inner surgical space; it was removed by partial exenteration.

Discussion

Orbital meningiomas are either primary or secondary depending on their site of origin. Primary meningiomas arise either from the cap cells of the arachnoid surrounding the nerve, that is, a primary optic nerve meningioma, or, more rarely, from cells external to the dura of the nerve but within the orbital periosteum, the 'extradural orbital meningioma' described by Craig and Gogela.²

Secondary meningiomas extend into the orbit from adjacent structures by expansion of the sphenoid or less commonly the frontal bone. Occasionally a meningioma may originate in the middle fossa and enter the orbit through the superior orbital fissure or extend down the optic canal and enter the orbit in the subdural space. This latter type of presentation accurately mimicks a primary optic nerve meningioma.

Primary optic nerve meningiomas can therefore be diagnosed only by accurately defining the origin of meningiomatous tissue found within the dural sheath of the optic nerve. The diagnosis is one

of exclusion, and it can be made only if the structures surrounding the orbit are normal. The clinical and radiological assessment of these patients must therefore be extremely thorough. Routine postero-anterior, lateral, and optic canal views augmented by axial hypocycloidal tomography will define the sphenoid bone, and high resolution CT scans will confirm these findings and often show the intracranial extent of a sphenoid meningioma. Occasionally carotid angiography may be needed to supplement these investigations. CT scanners can now show the orbital structures in both the axial and coronal planes and provide pictures of excellent definition, so that ultrasonic examination of the optic nerve has been superseded.

The predominant feature of optic nerve sheath meningiomas was early visual loss. Proptosis, when it occurred, was noticed later and was often of small degree. This type of presentation is in direct contrast to tumours which arise outside the dural sheath, for they usually cause considerable proptosis before compressing the optic nerve; the exception is an extradural tumour in the apex of the orbit. The reason for the difference is the site of origin and mode of growth of an optic nerve meningioma. The tumour arises between the dural sheath and the pia covering the optic nerve. As it grows it is confined by the tough dura and compresses the nerve, causing a dense central scotoma which usually spreads to the more peripheral parts of the visual field. This pattern of change is not universal, for 5 patients retained a visual acuity of 6/12 or better although 4 had peripheral field loss. Meningiomatous tissue probably produces visual field changes by a combination of pressure and interference with the blood supply to the optic nerve, for decompression of the nerve did not prevent the visual deterioration progressing in any patient.

The spread of the meningiomatous tissue within the dural sheath has secondary effects on the optic nerve head. All patients had a swollen or atrophic optic disc when first seen, and in many cases opticociliary shunt vessels were present. Meningioma involved the optic nerve immediately behind the globe in those patients with opticociliary shunts.^{3,4} Occasionally forward extension of meningiomatous tissue is so extensive that it invades the optic nerve head.⁵

The restriction of movement of the eye seen in most patients is probably caused by splinting of the optic nerve by tumour spread within the dural sheath. It is difficult to explain why upward movement is especially affected. When the patient attempts to move the eye, there is often an accompanying rise in the intraocular pressure. This is probably caused by the vigorous contraction of the extra-

ocular muscles attempting to overcome the mechanical resistance provided by the thickened and abnormal optic nerve. The slight proptosis observed in many of the patients can be attributed to the straightening of the normal S shape of the optic nerve within the orbit. More marked proptosis occurs if the tumour ruptures through the dura and forms a space-occupying lesion within the muscle cone.

Two patients experienced intermittent loss of vision initially. In 1 (patient 14) vision was lost when the eye was abducted. Fluorescein angiography showed that the visual loss was caused by interruption of retinal arterial flow. Two factors were probably responsible for this. The meningioma was fibrous and surrounded the point of entry of the central retinal artery so that any movement of the eye constricted the artery. The splinting effect of the tumour also produced a rise in the intraocular pressure. Thus, the perfusion pressure within the artery was reduced and the external pressure on the central retinal artery increased. Despite a decompression of the optic nerve, together with a Scheie thermal sclerostomy to lower the intraocular pressure, the obscurations gradually became more prolonged and more easily provoked. After 12 months the eye became blind and the optic disc atrophic with opticociliary shunt vessels.

A peculiar effect of the spread of tumour within the dural sheath was seen in patient 18. At the initial operation the distention of dura by a large quantity of CSF was thought to be an arachnoid cyst.⁶ The patient's proptosis increased and the vision deteriorated further. During this time high resolution CT scanning had been developed, and this showed a mass in the apex of the orbit. A primary optic nerve meningioma was found surrounding the posterior third of the optic nerve. This had presumably caused CSF to accumulate in the anterior part of the subarachnoid space.

In a previous report from this hospital⁷ attention was drawn to the infrequency of optic nerve meningiomas in children. In that communication the only child was a boy of 11 who was originally diagnosed as having a primary optic nerve meningioma by an ophthalmologist, who removed the boy's left eye because it was blind and grossly proptosed. Meningiomatous tissue surrounded the excised optic nerve. Three years later, when he was first seen in this clinic, meningioma was present in the middle cranial fossa and was affecting his right optic nerve. During the past 4 years the tumour has extended into the right orbit subdurally and has also involved the chiasm, so that he is now blind. The origin of this tumour is therefore uncertain, for it could have originated on the planum sphenoidale and spread down both optic nerves rather than beginning in

the left optic nerve sheath.^{3,4} The patient has not been included in this present series. A number of similar 'bilateral optic nerve meningiomas' have been seen during the period of this survey. In several there was radiological evidence that the tumour originated on the planum sphenoidale with subsequent subdural spread into each orbit. A report on the clinical and radiological features of this group of meningiomas is in preparation.

The age range and sex ratio of our patients corresponds very closely with those of other clinical series.^{2,5,9} These have shown that primary optic nerve meningioma occurs predominantly in middle aged women and is rarely encountered in children. Karp *et al.*¹⁰ reporting 25 patients considered to have a primary optic nerve meningioma found that 40% of their cases occurred in children and young adults below the age of 20. They concluded that primary optic nerve meningioma was less rare in children than has been generally assumed. It is difficult to reconcile their statistics and conclusions with our experience and that of others. It is possible that during the 40-year period of their study specimens from 10 children with definite primary optic nerve meningiomas were sent to the laboratory, whereas only a small proportion of tumours occurring in adults were referred. The selection of only 21 cases from a total of 81 on file at the registry could also have influenced the statistics. Another possibility is that the meningiomatous tissue encountered in the orbit may not have originated in the optic nerve. The pathologist is dependent on the accuracy of the clinical details and diagnosis supplied by surgeons, who may be unfamiliar with orbital disease. Some of the patients detailed by Karp and his associates were first seen at a time when investigative methods were comparatively primitive, and the clinician could not have been sure of the site of origin of the original tumour or the recurrences which occurred in 6 of the children.

That optic nerve meningiomas do occur in children is beyond doubt. A number of well documented cases have been recorded by several authors. Walsh¹¹ reported 7 children with this lesion with local recurrence and extension into the optic canal in several patients. He thought that these tumours were aggressive and often heralded the development of central neurofibromatosis. He suggested that diagnosis of the condition was often delayed because a child, particularly one with neurofibromatosis, would be assumed to have a glioma affecting the nerve. He therefore advocated doing a biopsy to differentiate between the two conditions.

Patients with a primary optic nerve meningioma should have a good prognosis, for the tumours are peripheral, slow growing, and isolated from the

central nervous system. Henderson⁸ has reported 9 adults with survival up to 19 years after the initial diagnosis was made. Two patients not included in our series have been treated conservatively without biopsy because the patients were elderly and there was little proptosis. One has shown no change over a period of 8 years.

Surgery in the patients reported in this paper has been directed towards total removal of the meningioma once useful vision had gone; biopsy and decompression of the optic nerve where vision remained; or, if there was a small anteriorly located tumour, its total removal with preservation of vision. A dilemma arises in judging whether to explore the affected optic nerve once the provisional diagnosis has been made. If the eye is blind, removal of all the meningiomatous tissue prevents growth of the tumour within the orbit or along the optic canal to the chiasm and should improve an already favourable prognosis. If useful vision remains, incising the dura should relieve the pressure of the tumour on the optic nerve. The results of this procedure have, however, been disappointing. In all patients the visual deterioration continued and useful vision was destroyed within 18 months, so that another lateral orbitotomy was required to excise the meningioma. In 1 patient (case 20) the attempt at decompression probably allowed the tumour to spread widely into the posterior half of the orbit, so that an exenteration will be needed in the near future to remove a tumour which was previously locally resectable.

We now believe that the most appropriate management for patients with relatively good vision is to wait for vision to deteriorate and then excise the optic nerve together with the meningioma. Biopsy or any surgery which transgresses the dura should be avoided. There are 2 exceptions. First, if the rate of growth of the optic nerve tumour suggests a malignant type of meningioma, the tumour should be biopsied. Secondly, if high resolution CT scans show a small, very anterior tumour and useful vision remains, the nerve should be explored, for this type of lesion can be removed without destruction of vision as in patient 2. The results of the type of treatment we advocate can be judged only with a follow-up of very many years.

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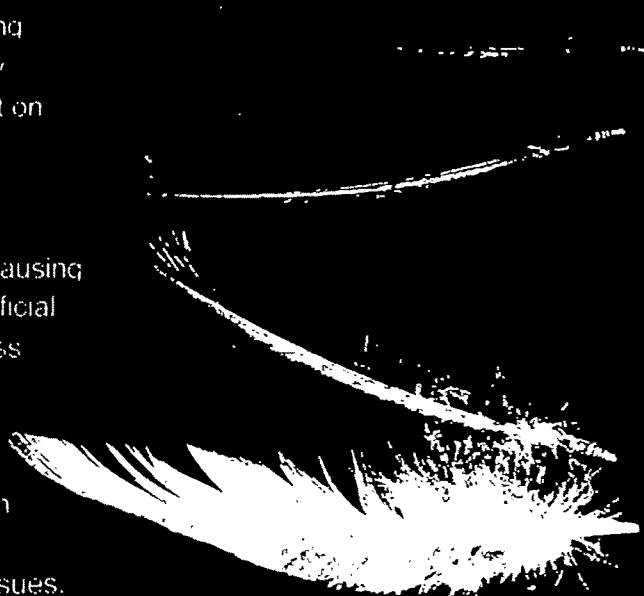
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Human chorioretinal biopsy under controlled systemic hypotensive anaesthesia

I. J. CONSTABLE, G. H. CHESTER, R. HORNE, AND J. F. HARRIOTT

From the University of Western Australia and Royal Perth Hospital, Perth, Western Australia

SUMMARY This paper describes a simplified technique for biopsy of the retina and choroid which had been used in 5 human volunteers. The biopsy was carried out in 4 immediately before enucleation of an eye for malignant melanoma and in 1 patient who was undergoing trabeculectomy for painful glaucoma associated with retinitis pigmentosa. A combination of intravenous mannitol and transient controlled systemic hypotension, induced under general anaesthesia with intravenous sodium nitroprusside, was used in 3 cases and resulted in no vitreous loss and minimal bleeding. In the 2 cases in which hypotension was not used bleeding was a definite problem, but no vitreous loss was experienced.

Understanding of many types of chorioretinal pathology has long been retarded by the lack of a practical biopsy technique. Previous workers have described a full-thickness eye wall method for biopsy of the posterior segment in rabbits, monkeys, and 1 human.^{1–3} A transvitreal approach to retinal biopsy has also been reported in animals.⁴ These methods have not been widely adopted because of the complexity of the procedure and of the universal vitreous loss reported. A simplified trans-scleral approach to chorioretinal biopsy in dogs using hypotensive anaesthesia resulted in minimal or no vitreous loss,⁵ so that we were encouraged to apply the procedure to 5 human volunteers.

Patients and methods

CASE 1

A 35-year-old male presented to the neurology outpatients with a 6-week history of blurred vision in the left eye. Vision was 6/6 right, counting fingers left, and a superior field defect was noted in the left eye. On referral to the ophthalmology department a large serous detachment of the inferior retina in the left eye was noted as well as an underlying pigmented mass that had the clinical characteristics of a large melanoma of the choroid. Fluorescein angiography, ³²P isotope testing, and ultrasonography all suggested a melanoma of the

choroid. The lesion was judged to be too large for local radiotherapy or photocoagulation and enucleation was advised. A systemic survey for metastases was negative. Appropriate patient consent was obtained. A local chorioretinal biopsy in the upper temporal quadrant in the area of attached retina was planned immediately before enucleation of the patient's left eye. A spindle cell B melanoma was confirmed.

CASE 2

A 45-year-old female was referred with a 3-month history of blurred vision in the right eye in August 1978. Her general health had been previously excellent. On examination there was a large collar-stud mass occupying the midperipheral area of the inferior retina. It was pigmented and approximately 6 disc diameters in size. There was a surrounding serous detachment which extended to the fovea. Fluorescein angiography, ³²P uptake, and ultrasound were all positive for melanoma. Vision was reduced to 6/12 right eye. The left eye had 6/5 vision and no abnormalities. The mass was considered too large for local treatment, and enucleation of the right eye was recommended. On 8 September 1978, with appropriate patient consent, a chorioretinal biopsy was carried out before right enucleation. Histology confirmed an epithelioid melanoma of the choroid.

CASE 3

A 45-year-old man presented to the ophthalmology department in February 1979 with a 4-month history of blurred vision centrally in the left eye.

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His general health had been previously excellent. Vision was 6/5 right, 6/60 left. There was a large raised pigmented mass 4 disc diameters in area at the posterior pole of the left eye. It was surrounded with a thin layer of subretinal fluid. Fluorescein angiography and ^{32}P uptake were both positive for melanoma. No evidence of systemic metastases was found on routine surveys. Enucleation was recommended for the left eye because of the size, position, and surrounding subretinal fluid associated with the tumour. Permission was obtained for chorioretinal biopsy, and this was carried out under general anaesthesia immediately before enucleation on 14 March 1979. A spindle cell B melanoma was confirmed.

CASE 4

A 70-year-old man was found to have a raised pigmented mass in the inferonasal quadrant of the right eye on routine examination by his ophthalmologist in 1974. This was followed at regular intervals until May 1979, when the patient presented with sudden loss of vision in the right eye associated with vitreous haemorrhage. The patient had been admitted to hospital with a myocardial infarct in January 1978 but had made an excellent recovery and has now considered to be in reasonable general health. Enucleation of the right eye was advised after consultation with several ophthalmologists, and permission was obtained to carry out a chorioretinal biopsy immediately before this procedure. In this case controlled hypotensive anaesthesia was withheld because of the patient's age and history of ischaemic heart disease. Pathology confirmed a spindle cell B melanoma.

CASE 5

A 68-year-old woman presented to the ophthalmology outpatient department in July 1978 with a painful blind right eye and vision reduced to counting fingers in the left. The patient had a history of retinitis pigmentosa with poor night vision and constricted visual fields by the age of 20. There was no family history of the disease. The patient was declared legally blind in 1968 at the age of 57 and was admitted as a chronic patient to the Braille hospital. She had a 5 year history of mild maturity onset diabetes and was also on digoxin and diuretic for congestive cardiac failure. On examination the right eye had marked central corneal oedema, a narrowed anterior chamber, and a closed angle. The lens showed moderate nuclear sclerosis but no signs of intumescence. No view was obtained of her fundus. Intraocular pressure was 50 mmHg right, 15 mmHg left eye. The left eye showed nuclear sclerosis of the lens and end-stage retinitis pigmen-

tosa. On gonioscopy the left angle was narrow but open. The patient was treated for 3 months with pilocarpine drops and systemic acetazolamide. She continued to have intermittent pain in the right eye and was often distressed with vomiting. She was admitted to hospital on 29 September 1978 with congestive cardiac failure. This responded to increase in the diuretic regimen, and the patient was again discharged. Treatment for the chronic glaucoma in the right eye was continued, but pain and discomfort did not subside. The patient was then readmitted on 29 November 1978, at which time the blind right eye was still painful. There was persistent right corneal oedema. Intraocular pressure was 50 mmHg right, 12 mmHg left. On 1 December 1978 a right trabeculectomy was planned for the chronic closed-angle glaucoma. Permission was obtained from the patient to carry out a chorioretinal biopsy at the same time. Again no hypotensive anaesthesia was used. On the third postoperative day the patient developed intermittent paroxysmal tachycardia and signs of pulmonary oedema. Despite therapy she failed to respond and died on the fourth postoperative day.

ANAESTHETIC TECHNIQUE

In cases 1, 2, and 3 intravenous mannitol 1 g/kg was given 20 minutes before retinal biopsy to soften the eye and decrease the vitreous volume. At the time of biopsy transient systemic hypotension was also induced. Preoperative anaesthetic assessment excluded cardiovascular and respiratory disease. The electrocardiogram was normal in these 3 cases, as was blood count and chest x-ray. Premedication was confined to 25 mg promethazine HCl intramuscularly 1 hour before induction of anaesthesia. Standard anaesthetic induction included preoxygenation, thiopentone 300 mg intravenously, muscle paralysis with intravenous suxamethonium pretreated with D-tubocurarine, and lignocaine spray to the vocal cords. A cuffed Oxford tube was placed in position, and anaesthesia was maintained with nitrous oxide 3 litres/minute, oxygen 1.5 litres/minute, and 1-2% halothane on a semiclosed circuit. The ECG was monitored continuously, and brachial blood pressure was monitored on both arms with an oscillometer. An intravenous line for infusion of mannitol was placed in the left arm; a second intravenous line was placed into a dorsal vein in the left foot for infusion of sodium nitroprusside. This latter intravenous drip was set up with 30 mg sodium nitroprusside in 500 ml of 5% dextrose. A trial dose of sodium nitroprusside was infused early in the operation to test the patient's individual response. In case 1 it was found that systolic blood pressure was difficult to lower

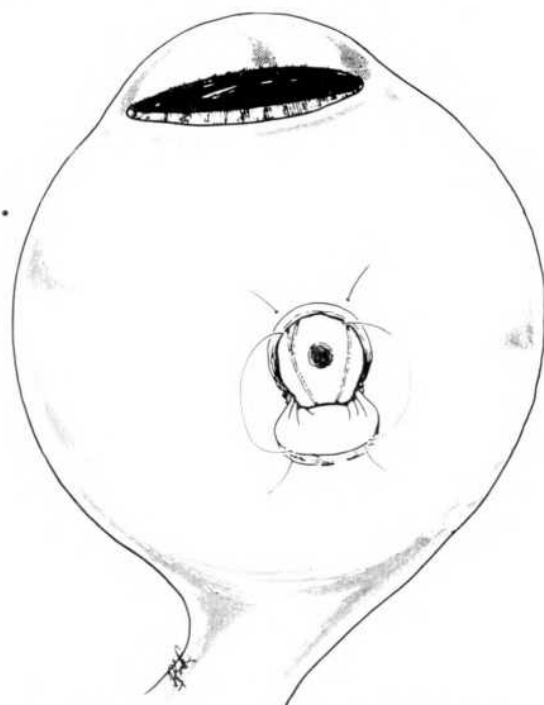


Fig. 1 Schematic drawing of chorioretinal biopsy site in a human eye.

below 80 mmHg owing to a persistent tachycardia of 90/minute. The patient was therefore given practolol 1 mg intravenously, which reduced the pulse rate to 65/minute. Immediately before the final steps in the chorioretinal biopsy the sodium nitroprusside infusion was allowed to drip slowly so that the systolic blood pressure was lowered to 70 mmHg over 2½ minutes. This level was maintained with continuous infusion over 5 to 10 minutes during which time the biopsy was taken. A total of 60 to 80 ml of infusion containing 3.6 to 4.8 mg sodium nitroprusside infused at the rate of approximately 8 µgm/kg/minute was used in each case. At the end of the biopsy the sodium nitroprusside drip was turned off, and blood pressure returned to normal levels under anaesthesia within 3 minutes.

In cases 4 and 5, because of age and history of cardiovascular disease, intravenous mannitol and sodium nitroprusside infusion were withheld. In both cases the general anaesthesia was induced with 150 g of thiopentone after preoxygenation, and intubation was carried out after 10 mg suxamethonium and lignocaine spray to the vocal cords. Maintenance was with a nitrous oxide/oxygen mixture in a 3:1 ratio. Intermittent enflurane, droperidol (total 5 mg), phenoperidine (0.5 mg), and alcuronium chloride (10 mg) were given during the procedure. Acetazolamide (500 mg) was given

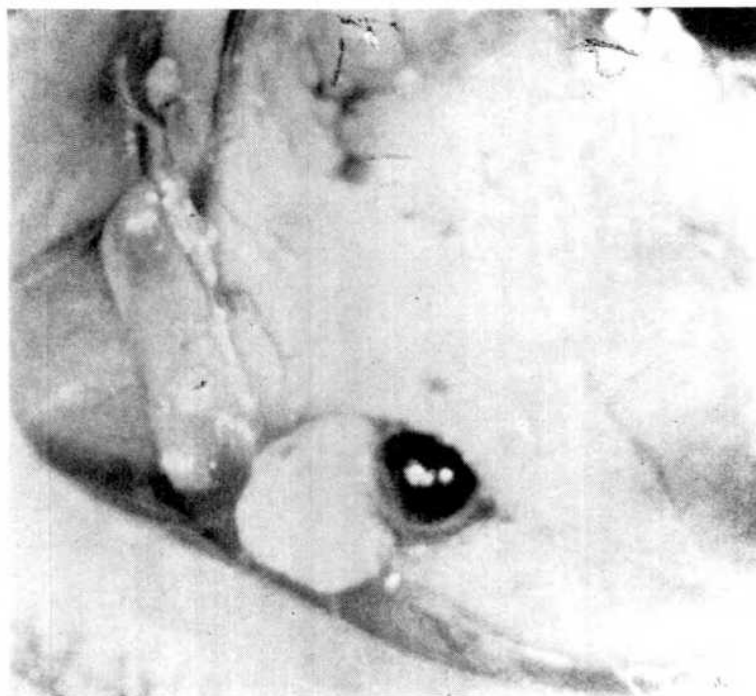


Fig. 2 Intact vitreous face after chorioretinal biopsy. Print taken from a 16 mm film.

intravenously to lower intraocular pressure during the procedure.

SURGICAL TECHNIQUE

After conjunctival peritomy and placement of bridle sutures a biopsy site was selected in the superior temporal quadrant posterior to the equator, except in case 3, in which an upper nasal site was selected. In each case the site selected was overlying attached retina on the opposite side of the globe to the melanoma.

The exact site was chosen clear of major vortex

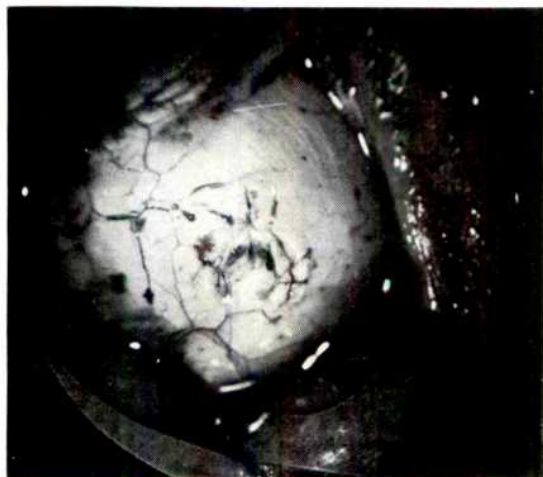


Fig. 3 Full-thickness scleral flap closed with interrupted 8-0 Vicryl sutures after chorioretinal biopsy.

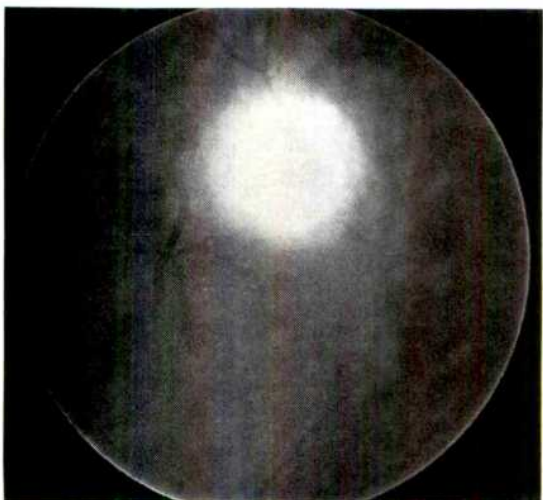


Fig. 4 Fundus photography of biopsy site immediately after closure of the scleral flap and prior to enucleation of the eye in case 1. There is no evidence of bleeding and no elevation of the surrounding retina.

veins after transillumination of the globe. A full-thickness, circular, 270° scleral flap of 3 mm diameter was then raised (Fig. 1). Two 8-0 Vicryl sutures were placed through the flap and the host bed of sclera to facilitate closure after chorioretinal biopsy. The site was again transilluminated to select the area for biopsy in between larger choroidal vessels. At this stage the sodium nitroprusside infusion was started in the first 3 cases described and this visibly blanched the choroid. The eye was already soft owing to infusion of mannitol 1 g/kg intravenously over the previous 20 minutes. When systolic blood pressure was reported by the anaesthetist to be lowered to a level of 70 mmHg, a biopsy was taken with blunt jeweller's forceps and small curved Vannas scissors. The choroid and underlying retina were slightly tented with the grasp of the forceps, and the first cut exposed the vitreous face. After inserting one blade along the vitreous face the biopsy was excised with 2 more cuts. It was immediately placed in glutaraldehyde and the instruments were changed for closure of the wound. In all 5 cases the vitreous face bulged, but none was lost (Fig. 2). In cases 4 and 5, in which mannitol and hypotensive anaesthesia were withheld, there was excessive choroidal bleeding, which meant that a fragmented biopsy was obtained. The scleral flap was closed with the preplaced sutures (Fig. 3). In cases 1 to 4 before enucleation of the globe photographs were taken of the biopsy site with a portable Kowa fundus camera (Fig. 4). In case 5 the eye was not removed but a routine trabeculectomy was carried out in the superior temporal quadrant under a limbal based scleral flap.

Discussion

The 3 younger patients submitted to transient hypotensive anaesthesia tolerated the procedure well and showed no postoperative side effects. Case 5 unfortunately developed acute pulmonary oedema 4 days postoperatively and died. After careful investigation it was concluded that the anaesthetic itself and the surgery were unlikely to have been the direct cause, but that they might have contributed to the final cardiovascular decompensation.

Of the 5 biopsy specimens of the choroid and retina obtained only 3 were entirely satisfactory for electron microscopy. The specimens tended to roll up on the end of the forceps when placed in fixative, and it was difficult to prevent artefact detachment of the retina from the pigment epithelium. However, in 3 cases good individual specimens were obtained (Fig. 5). High power examination of these specimens confirmed good fixation and good resolution of detail at the base of the pigment epithelium and

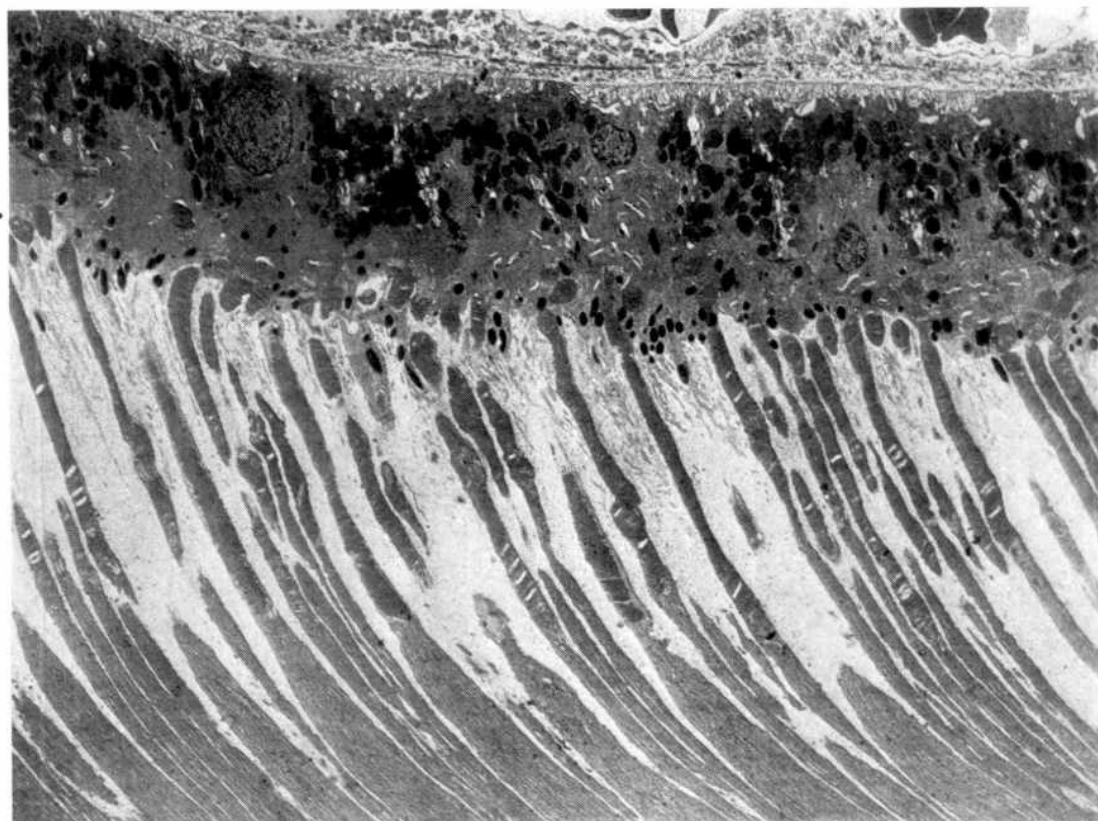


Fig. 5 Electron microscopic appearance of chorioretinal biopsy from case 1 showing some bending of outer segments and slight spreading of the receptor discs. The specimen is quite adequate for interpretation. ($\times 1880$.)

Bruch's membrane, the receptors and the internal limiting membrane of the retina respectively (Fig. 6). The poor specimens were obtained from the 2 eyes in which hypotensive anaesthesia was not employed. Because of the bleeding it was not possible neatly to excise the biopsy specimens, and indeed they were removed piecemeal because of the risk of cutting into the vitreous face in the presence of blood. However, individual cell layers could be assessed in these 2 specimens. It is to be noted that renal and liver biopsies are often less than ideal.

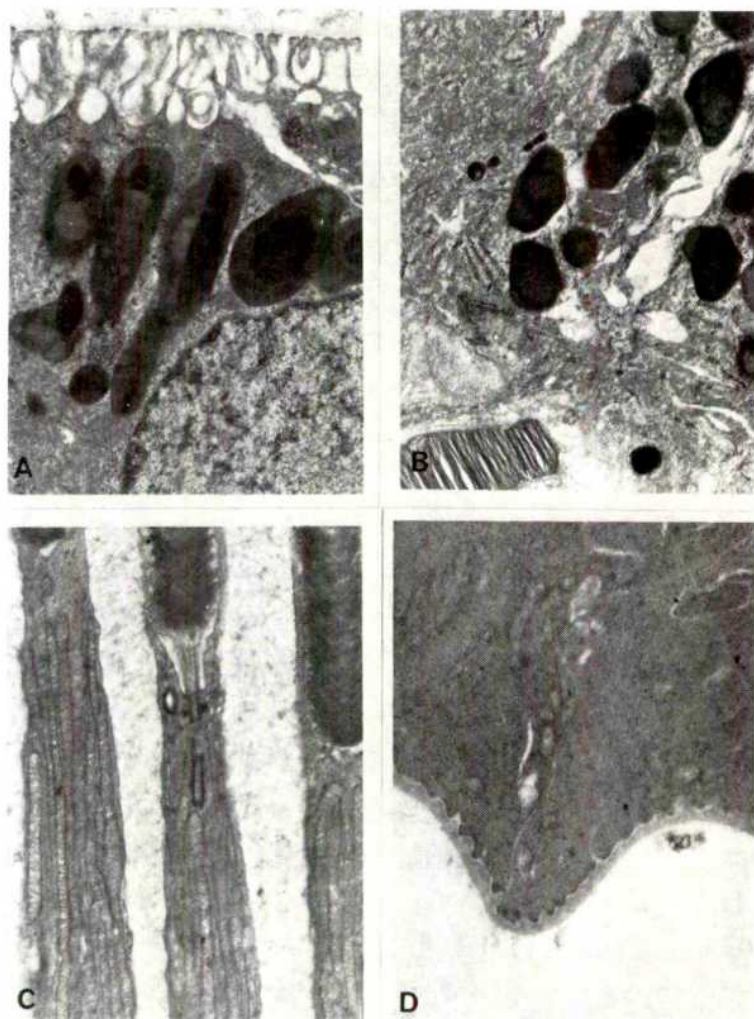
The choroidal bleeding was surprising in the case of the eye with end-stage retinitis pigmentosa. It had been presumed that, because of choroidal and retinal atrophy, bleeding would not be a problem.

Nevertheless even in the cases not subjected to ocular and systemic hypotension it was shown that choroid and retina could be excised without losing vitreous. It is suggested that, if the problems of handling such minute specimens of choroid and retina can be overcome, this technique may have widespread application, particularly in young

patients in whom controlled hypotensive anaesthesia can be employed without significant risk. In this context it is to be noted that sodium nitroprusside infusion is used to induce transient hypotension in a wide variety of surgical fields, notably vascular, cerebral, and cardiac surgery. In these areas the hypotension is often maintained for long periods without ill effects. In the case of retinal biopsy it is necessary for only 5 to 10 minutes.

It is obviously of great importance to determine whether excision of a 1 mm piece of choroid and retina without disturbance of the vitreous face would lead to retinal detachment in humans in the short term or long term. To date, the definitive experiment, which would require a volunteer to submit a blind eye perhaps from optic atrophy to the procedure, has not been carried out. It is noteworthy, however, that retinal detachment must be extremely rare in patients with retinal dystrophies, as we have been unable to extract any reports from the literature or from anecdotal sources to date. It is possible in those patients who have widespread pigment

Fig. 6 Composite higher-power electron micrographs of human chorioretinal biopsy specimen. (A) Basal section of retinal pigment epithelial (rpe) cell ($\times 8640$). (B) Apical section of rpe cell ($\times 7808$). (C) Junction of inner and outer segments of rods ($\times 10\,000$). (D) Inner surface of retina showing internal limiting membrane ($\times 11\,200$).



epithelial disturbances that the risk of retinal detachment is minimal because of pathological retinal adhesion.

If this simplified chorioretinal biopsy technique can be shown in a large number of cases to be free of the dual risks of massive haemorrhage and significant vitreous loss, then a wide range of laboratory techniques could be employed to elucidate chorioretinal diseases at present poorly understood.

We thank Dr D. C. Wilson for referring two of the cases, Mr C. Barry for clinical photography and Miss H. Dedy for secretarial help.

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Pattern of mortality in choroidal malignant melanoma

R. B. S. PACKARD

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SUMMARY A large series of cases of malignant choroidal melanoma has been reviewed. Certain risk factors have been related to prognosis by means of actuarial life tables. With information from these tables to calculate mortality rates graphs were drawn for various risk factors to demonstrate the differing pattern in tumours of varying size, degree of pigment, position of anterior border, etc. Further, a discriminant analysis was carried out in relation to differing cell types of tumour. It was concluded that tumour size overall was most important for assessing prognosis, and for small tumours the type of treatment seems not to influence survival. The presence of an early mortality peak is found, as suggested in other series, but a second peak is also present. A possible cause of this later peak is suggested.

Since the earliest descriptions of pigmented tumours at the beginning of the 19th century,¹ and of ocular tumours of this nature in particular, controversy has existed as to the histogenesis, behaviour, clinical course, and treatment of choroidal malignant melanoma. The most recent of these disputes has been that arising from the publications by Zimmerman and colleagues.²⁻⁴ These writers having initially stated that 'It cannot be concluded that there is a group of favourable cases (of malignant choroidal melanoma) for which enucleation is excessive treatment'. Then in a later article they looked again at the data of Paul *et al.*⁵ From this new analysis they arrived at certain impressions: (1) that the mortality rate before enucleation is low, (2) that the mortality rate rises abruptly following enucleation, (3) that approximately two-thirds of the fatalities could be attributed to the dissemination of tumour emboli at the time of enucleation.³ In a subsequent article⁴ these writers expanded on the evidence to support these postulates.

As part of a study⁶ of a large series of choroidal malignant melanomas which was under way at the Institute of Ophthalmology at this time I subjected our available data to a more exhaustive examination of mortality patterns. This was in an attempt to throw further light if possible on this matter. New material will also be presented here in relation to the type of treatment used and its effect on mortality.

Material and methods

The cases of malignant melanoma of the choroid on which this study was based were those seen and treated at Moorfields Eye Hospital between 1949 and 1972. By not including any more recent cases a minimum period of 5 years' follow-up was possible. This follow-up was carried out at Moorfields Eye Hospital at the City Road or High Holborn Branches, or by the referring hospital, or, finally, by letter via the patient's general practitioner. In those cases that died the cause of death was either discovered directly from the Cancer Registry at the Institute of Ophthalmology following notification by the hospital or general practitioner concerned, or in some cases a relative supplied notification of death and later the cause was sought from the Registrar General's records. All available information regarding the patients was stored in the card index of the Cancer Registry at the Institute of Ophthalmology.

In cases where the information was incomplete with regard to such things as length of history prior to treatment the patient's notes were obtained from the files at Moorfields Eye Hospital. By far the largest part of the series consisted of patients who had been treated by enucleation as a primary procedure. The total number of cases was 578, of whom 506 had had enucleation. Of these 506 patients 484 had their enucleations as a primary procedure, and 22 patients initially treated conservatively had either had continued tumour growth or complications from their treatment which had made enu-

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cleation necessary. As well as using the information obtained as above, the slides from the specimens obtained from these cases were examined to determine various pathological parameters which will be mentioned shortly. Between these 3 sources a reasonably full picture of the cause of the disease and its manifestations in individual cases could be reached for most patients.

In my thesis the following risk factors were analysed in a univariate and multivariate manner using the computer facilities at the University of London in order to try to determine the influence, if any, of individual factors on each other and the relationship of different factors to prognosis. These last factors in relation to prognosis will be considered in this paper. They were divided as follows:

(a) *Clinical features.* (i) Age of the patient at the time of treatment in years. (ii) The sex of the patient. (iii) The eye involved. (iv) The duration of history in months to the point of treatment. (v) The presence or absence of a blind, painful eye at the time of primary treatment.

(b) *Macroscopical features of the tumour.* (i) The largest dimension of the tumour (LTD) in millimetres was measured on the largest section available. (ii) The anterior and (iii) posterior margins of the tumour were noted on similar sections. This was divided into 3 groups (a) ciliary body to ora serrata, (b) ora serrata to equator, (c) posterior to equator.

(c) *Microscopical features of the tumour.* (i) The cell type of the tumour was determined according to the classification current at the Institute of Ophthalmology and consisting of A—pure and predominantly spindle cell tumours; B—mixed cell tumours where one-third or more cells were epithelioid in type, the rest being spindle; C—pure and predominantly epithelioid tumours; D—tumours so necrotic that accurate classification was impossible, though, as will be seen this in fact represents a very small percentage of the series as a whole. Such a classification first described by Ashton⁷ is very similar to that used by Raivio.⁸ (ii) *Pigmentation* was divided into 4 groups: A—amelanotic tumours or those with only a few widely scattered spots of pigment; B—lightly pigmented tumours where about 25% of the cells were obscured; C—if 50% of cells were obscured this was moderately pigmented; D—heavy pigmentation where 75% of the cells or more were unable to be seen without bleaching the section.

(iii) *Reticulin fibre content* was noted and classified in 4 groups. Wilder's staining technique was used here. A—no reticulin fibre present between cells; B—light fibre content where 25% of the cells were surrounded; C—moderate content if 50% of cells

were surrounded; D—heavy content if more than 75% of cells have reticulin surrounding them. (iv) *Scleral extension* was found most convenient for division into 4 also. A—no extension or only a minimal amount; B—quarter to half thickness extension; C—greater than half thickness extension; D—episcleral extension. (v) *Optic nerve extension* was assessed, but the numbers involved were very small and no useful conclusions could be drawn from these data. (vi) *The state of Bruch's membrane*, that is, whether ruptured or intact, was also noted.

(d) *Therapeutic features.* The next group of risk factors related to various aspects of treatment. The patients were divided into those having primary or secondary enucleation and those being treated conservatively. The vast majority of this latter group had treatment with local irradiation using radioactive plaques. It was hoped in the light of the report from Shamma and Blodi⁹ that the role of exenteration might be determined, but so few patients were treated in this way that no useful conclusions could be reached for this series.

In order to study prognosis, the survival time both from the start of the clinical history and from the moment of primary treatment were noted. The date taken for those patients who had not died to determine their survival was the end of 1977. Thus the status of patients at that date has been divided as follows: A—alive; B—dead from metastases from choroidal malignant melanoma; C—death from metastases from tumours other than malignant melanoma; D—death from causes not related to cancer.

After this, the prognosis was assessed in various ways. Firstly, cross-tabulation of various factors was undertaken against actual and percentage outcome in each case and an assessment of statistical significance using the chi-square test. In a second method, life tables were constructed as suggested by Berkson and Gage¹⁰ to allow the percentage survival after x years to be calculated with provision being made in the survival date for patients withdrawn due to death from other causes. By using these tables calculated for the various factors under consideration, their influence on prognosis may be seen in a univariate manner. Also the relationship to time and pattern of mortality can be noted in each instance. As well as the univariate analysis certain multivariate prognostic analyses were also made.

The data obtained by these means were put into graphical form in 2 ways—firstly to show the percentage survival in the years of the study and secondly to show changing percentage mortality, that is, the chances of dying in any year following the primary treatment. This latter part of the study

was similar to that carried out by Zimmerman *et al.*³ and also Benjamin *et al.*¹¹ and Jensen,¹² but the data under consideration were analysed in this manner for many different parameters.

Results

TOTAL NUMBERS

As already stated the series consisted of 578 patients with malignant choroidal melanoma. These were divided as follows as regards treatment: group I, primary enucleation, 484 patients (83.7%); group II, primary conservative with later enucleation, 22 patients (3.8%); group III, primary conservative, 72 patients (12.5%).

Of the group III patients, only 2 patients were observed with no treatment mode being employed, both of these patients died—one of unrelated causes and one who had presented with established melanoma metastatic disease died from these metastases. There were 2 other patients in the series as a whole who had established metastatic disease with a choroidal melanoma as the assumed primary at the time of diagnosis.

PROGNOSIS

Although as part of the doctoral thesis on which this paper is based prognosis was assessed by both cross-tabulations of risk factors in a single and multiple variate manner, the results were considered not as useful as those obtained by the use of actuarial life tables, and these alone will be presented here. This method allowed for the cases being withdrawn because of death from other causes and also for patients who were not followed up for the whole period under review to be included. This actuarial method of assessing outcome was also used by Shamma and Blodi.⁹ It has the added value of providing not only figures for survivors but also the chances of a patient dying in any given year following primary treatment. Using this method also will avoid any criticisms of the sort levelled by Siegel *et al.*¹³ at Zimmerman and McLean⁴ for their use of statistics from Paul *et al.*⁵

Whole series. With the use of life tables as shown in Table 1 the series as a whole was assessed. The actuarial survival curves will be considered first. It will be seen from the graph (Fig. 1) that the overall survival rates were 78.7% at 5 years, 66.2% at 10 years, and 61% at 15 years. This is somewhat better than the figures of Paul *et al.*⁵ who used an actuarial method of calculating their results (71% at 5 years, 60% at 10 years, and 46% at 15 years). It will be seen when Fig. 1 is considered also that the non-enucleated group fared rather better than the enucleated group. The reasons for this will be

Table 1 Life table for survival after treatment all patients

Interval in years	During interval		Living at start interval	Adjusted no. at risk	Prob. of death from MM	Percentage survivors at end of interval
	Died	With-drawn				
0—	15	7	576	573	0.0262	97.4
1—	22	4	554	552	0.0399	93.5
2—	31	8	528	524	0.0592	88.0
3—	34	8	489	485	0.0701	81.8
4—	17	8	447	443	0.0384	78.7
5—	14	34	422	405	0.0346	75.9
6—	13	19	374	365	0.0357	73.2
7—	7	30	342	327	0.0214	71.7
8—	10	14	305	298	0.0336	69.3
9—	12	22	281	270	0.0444	66.2
10—	4	25	247	235	0.0171	65.1
11—	2	28	218	204	0.0098	64.4
12—	4	20	188	178	0.0225	63.0
13—	1	24	164	152	0.0066	62.6
14—	3	20	139	129	0.0233	16.1
15—	2	21	116	106	0.0190	59.9
16—	4	13	93	87	0.0462	57.2
17—	1	8	76	72	0.0139	56.4
18—	0	10	67	62	0.0	56.4
19—20	1	14	57	50	0.0200	55.2

MM = malignant melanoma.

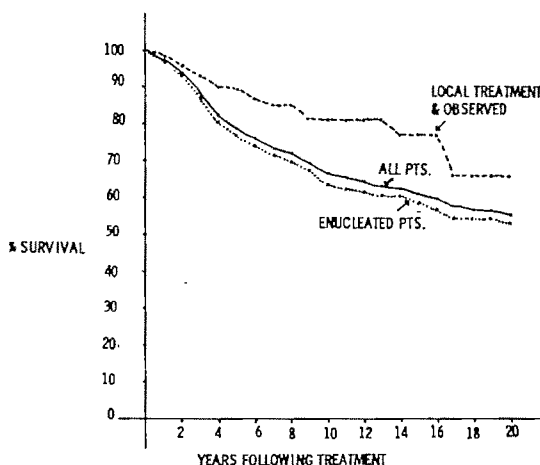


Fig. 1 Actuarial survival curve for patients with choroidal malignant melanoma.

discussed below.

Sex. There was a small survival difference between the sexes in that males seemed to survive better (at 10 years, males 69.2% and females 62.2% survival) than the females. There is no very ready explanation for this except possibly the higher incidence of heavy pigmentation in the older females. No similar relationship was found by Paul

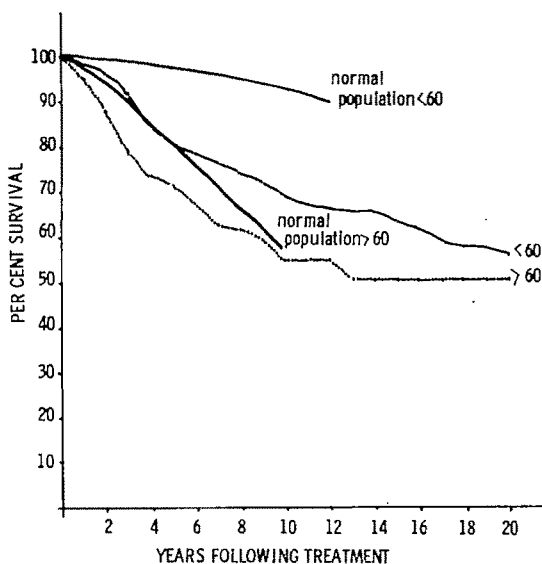


Fig. 2 Actuarial survival curve for patients with choroidal malignant melanoma over and under 60 years age groups.

*et al.*⁵ or Shamma and Blodi.⁹

Age. If the population under review is divided into groups over and under 60 years of age (Fig. 2) there is a general trend for those patients under 60 years of age to survive better. However, if the normal actuarial survival for the whole population is introduced, it will be seen that, while survival in the over 60s approaches that of a normal population, that of the younger group is much different. This would suggest that malignant choroidal melanoma is a more important factor in shortening life in patients under than over 60 years. This point will be clarified further when various other parameters are considered in conjunction with age.

Duration of history. On the duration of history the patients were divided into 2 groups, those with a history less than 1 year and those with a history of 1 year or more. The survival for both groups at 5, 10, and 15 years is really very similar for the 2 groups being at these 3 points, namely, 77.7%, 64.9%, and 60.8% for those with a shorter history and 74.5%, 60.9%, and 58.6% for the patients with a longer history.

Size. As already mentioned, tumours were divided for size into small, medium, and large. A survival curve (Fig. 3) shows the dramatic difference between these 3 groups.

Position of anterior border. If the position of the anterior border is divided simply into those with this border in front of and those behind the equator, there is a striking difference in survival. At 10 years

patients with anterior tumours have a 43.9% survival, while those with anterior borders posterior to the equator have a survival of 76.5%. These figures refer only to those patients who had undergone enucleation.

Cell type. Cell type of the tumour when assessed for prognosis Fig. 4 shows that spindle cell tumours have a much better prognosis (85% survival at 5 years) than either the mixed (58% at 5 years) or

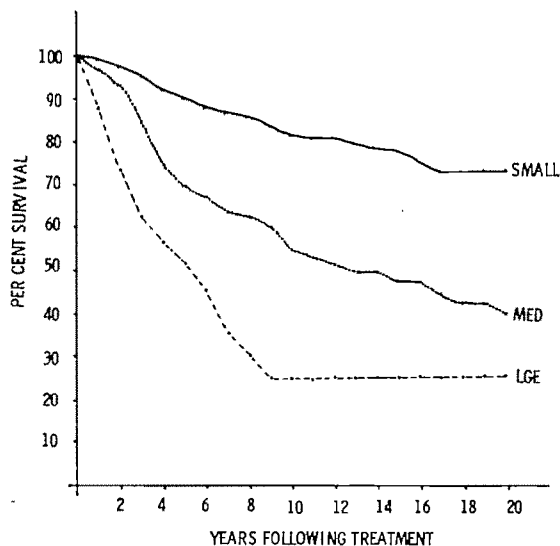


Fig. 3 Actuarial survival curve of patients with choroidal malignant melanoma for tumour size.

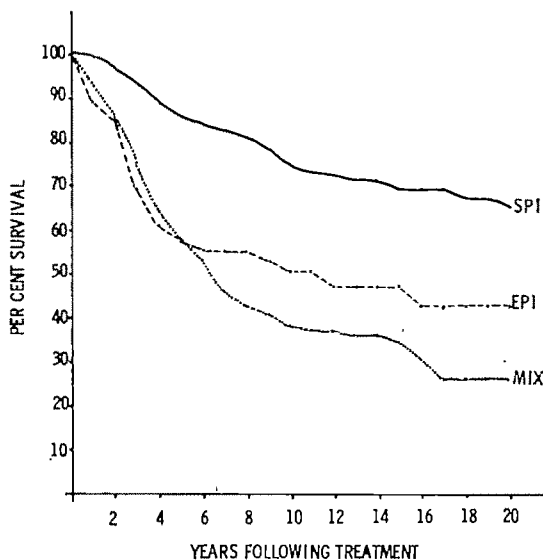


Fig. 4 Actuarial survival curve for patients with choroidal malignant melanoma for cell type.

epithelioid (57% at 5 years). The figures at 10 years suggest that patients with mixed cell tumours fare worse than those with epithelioid tumours. This is because epithelioid tumours in this series are relatively a small number and also they tend to occur in older patients. Thus this group was subject to a higher mortality from causes other than the tumour under discussion here.

Pigment content. Consideration of the level of pigmentation shows how much worse is the prognosis if the amount of melanin in the tumour is heavy. At 10 years the survival in these patients is 38.8% as compared to more than 75% in both amelanotic and lightly pigmented tumours.

Reticulin fibre content. In my thesis⁴ I found that for various risk factors there were no useful correlations for reticulin content. Indeed for prognosis an entirely different result from that found in other series is demonstrated with no reticulin (83.6% survival) given a better prognosis than heavy reticulin (53.9% survival) at 10 years. However, as will be seen later in the discriminant analysis, reticulin is not useful as a prognostic factor.

Scleral extension. This factor shows a marked difference between the increasing degrees of scleral extension (Fig. 5). Survival for those patients with no extension is really quite good (89.7% at 5 years, 81.7% at 10 years, and 76.4% at 15 years) as compared to patients with episcleral extension (42.3% at 5 years, 23.8% at 10 years, and 21.4% at 15 years). In fact all those patients who will die from their tumour are dead within 11 years of primary treatment where episcleral extension is present.

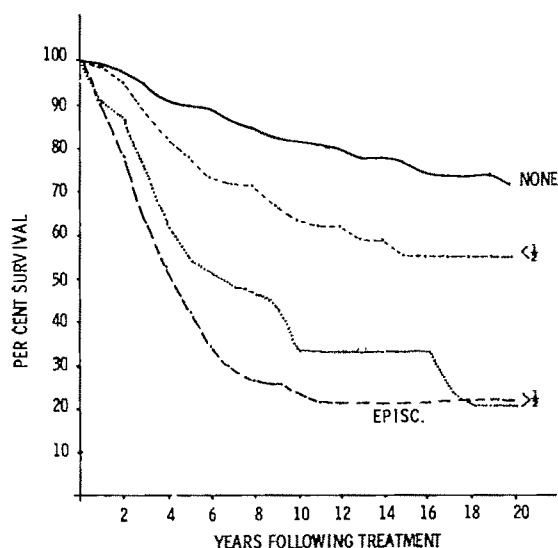


Fig. 5 Actuarial survival curve for patients with choroidal malignant melanoma for scleral extension.

A series of life tables were then constructed and graphs drawn from these to assess the influence of more than one factor on prognosis at any one time. Firstly age, either under or over 60 years at the time of primary treatment, was considered in relation to size, cell type, the presence of heavy pigment, and the presence of episcleral extension.

Age and size. The size of the tumour for the purposes of analysis here was recorded as being either less than or greater than 10 mm largest tumour diameter. When these 2 groups are combined with the 2 age groups plotted on a graph survival of both small tumour groups was very similar (83.5% at 10 years for the under 60s and 81.5% for the over 60s). The large tumour groups, however, had as expected a much worse prognosis, and the older patients of these 2 did the worst (54.3% survival at 10 years for the under 60s, 42.2% for the over 60s).

Age and cell type. A similar situation was found when cell type and age were considered in relation to prognosis in that spindle cell tumours in both age groups do quite well (at 10 years under 60s 76.4% survival, over 60s 69.4%) and mixed and epithelioid tumours (considered as one group) do considerably worse with the older patients surviving least well (at 10 years under 60s 49.9% survival, over 60s 24.4%).

Age and heavy pigment content. In this instance the difference between the age groups is quite large though in both the prognosis is poor (at 10 years, 47.5% survival for the under 60s and 27.0% survival for the over 60s).

Age and episcleral extension. All patients, as has been shown, have poor prognosis in this group, and the difference in survival seems unrelated to age, being at 10 years 23% for under 60s and 24% for over 60s.

State of Bruch's membrane. The state of Bruch's membrane when considered in isolation appears to have a profound effect on prognosis, i.e., at 10 years survival of 80.8% for those patients with an intact membrane and 55.8% where it is ruptured. In fact if the relationship of size to the state of Bruch's membrane is remembered, then the survival figures are almost certainly a function of the difference in size of the 2 tumour groups, Bruch's membrane intact and ruptured.

Next, size in the 2 groups as already mentioned and the variable cell type, presence of heavy pigmentation, and presence of episcleral extension were related in a life table and graphical form.

Size and cell type. In this combination it can be seen that, although size is very important within the different cell types themselves, mixed cell and epithelioid tumours have a worse prognosis than those with predominantly spindle cells. It is interesting

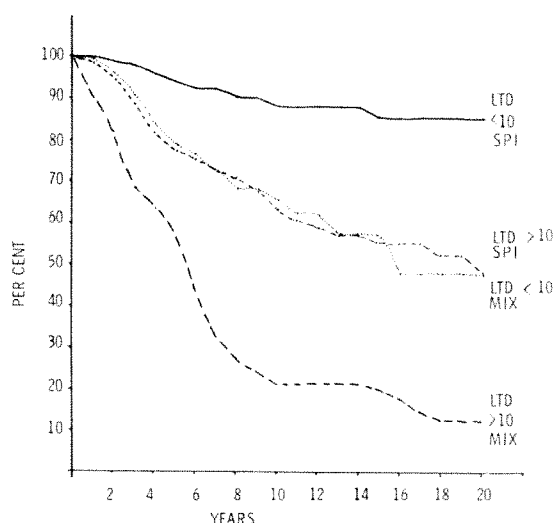


Fig. 6 Actuarial survival curve of patients with choroidal malignant melanoma when size and cell type are taken against prognosis.

that the larger spindle cell tumours and the smaller mixed cell tumours have an almost identical prognosis (Fig. 6).

Size and heavy pigment. Size showed itself to be important when taken with heavy pigment in that smaller tumours had a much better prognosis, i.e., 61% survival at 10 years as opposed to 27% for the larger tumours.

Size and episcleral extension. There was no such obvious difference between the size groups here, though whether this is a true relationship is uncertain because of the small numbers involved in the small size group with episcleral extension.

During the period that the doctoral thesis on which this study is based⁶ was being compiled, the ideas of Zimmerman *et al.* as first published in 1978 prompted a similar type of investigation into mortality rates using the present data.

The writers just mentioned had re-examined the data of Paul *et al.*⁵ and reworked them so that the rate of mortality from malignant choroidal melanoma was calculated in each year following primary treatment. In the cases used in their data their patients had all had enucleation. Zimmerman *et al.*³ and Zimmerman and McLean⁴ have postulated that, because these tumours had been growing for varying lengths of time prior to diagnosis, and in view of the seemingly similar prognosis after enucleation despite the length of history, combined with the knowledge of the rarity of metastasis being observed prior to enucleation, the peak in mortality rates which they have demonstrated in the years

immediately following enucleation may in some way be connected to this form of treatment. They felt that this rise in the mortality rate was due to dissemination of malignant cells at the time of surgery. Later writers¹³ have questioned firstly the existence of this mortality peak, by pointing out the inaccurate (statistically speaking) use of data by Zimmerman and colleagues and then the unique nature of this curve in relation to malignant choroidal melanoma. In view of these conflicting views I felt that the study I had undertaken could help to throw some further light on this vexed matter.

Accordingly graphs were drawn from the life tables used to calculate the survival data. This was done not only for the series as a whole, but also for various single and combinations of risk factors thus allowing a closer assessment of the influence of these factors on the time course of prognosis.

In the first graph (Fig. 7) is recorded the annual likelihood of mortality for the whole series, enucleated patients and those treated by conservative means.

Considering the whole series in the first instance, there would appear to be 2 peaks in mortality—one at 3–4 years following treatment and the other at 9–10 years. A similar shaped graph is obtained from those patients undergoing enucleation, but for the patients treated conservatively a much less definite pattern is seen. Although Zimmerman *et al.*⁴ chose to ignore the second peak, it is present on their graph and also that of Benjamin *et al.*¹¹ and Jensen.¹² The significance of the second peak will be discussed below.

The following risk factors were analysed individually to assist the influence on mortality rates which they might have and to demonstrate the

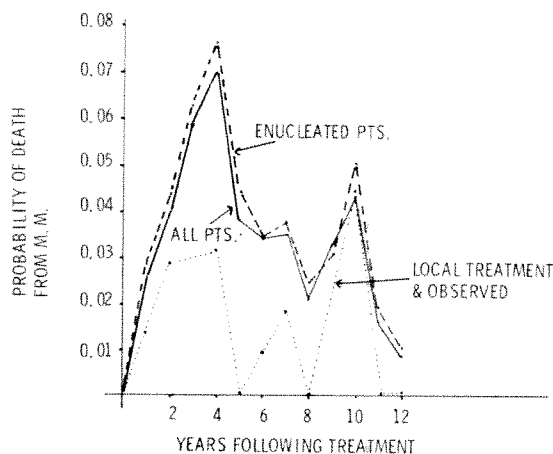


Fig. 7 Probability graph for death from choroidal malignant melanoma for all treatment groups.

varying patterns for different tumours—duration of history, position of the anterior border, tumour size, cell type, scleral extension; also age, at greater or less than 60 years in the presence of tumours larger or smaller than 10 mm (Figs. 8, 9, 10, 11, 12, 13).

The duration of history was for those patients with histories less than or more than 1 year. As can

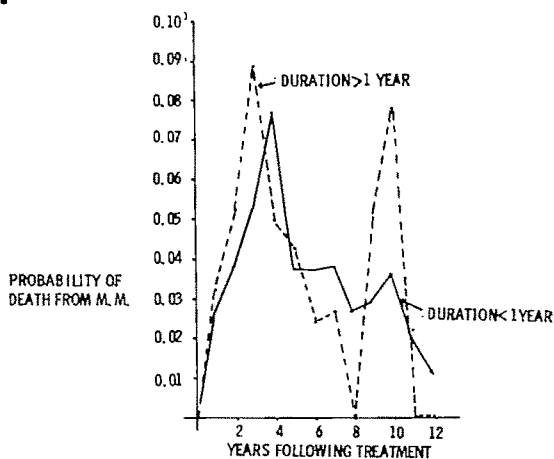


Fig. 8 Probability graph for death from choroidal malignant melanoma for duration of history.

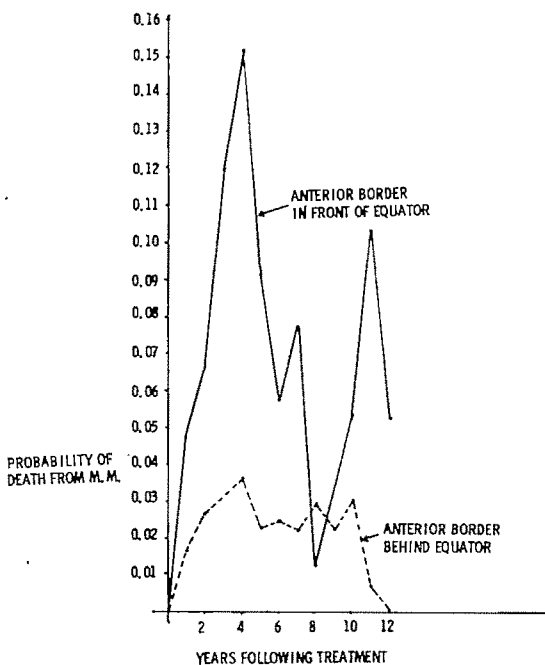


Fig. 9 Probability graph for death from choroidal malignant melanoma for position of the anterior border of the tumour.

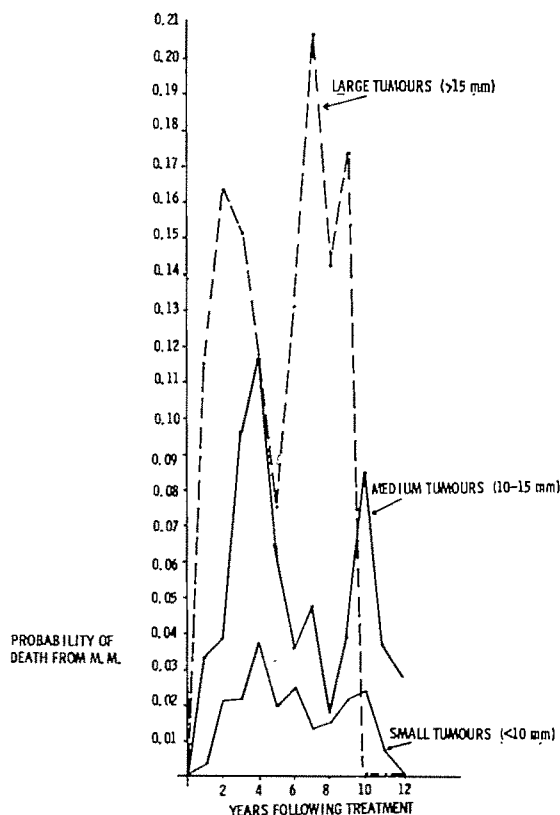


Fig. 10 Probability graph for death from choroidal malignant melanoma for tumour size.

be seen the mortality peak occurred 1 year earlier in those patients with the longer history. This was probably related to the patient's age more than anything else, because we know that the over 60s tend to have longer histories and they also have an earlier mortality peak.

Tumours with anteriorly placed borders have a much more dramatic mortality pattern than those with this border posterior to the equator (Fig. 9). In fact the pattern for these posterior tumours was very similar to that for small tumours (Fig. 10) spindle cell tumours (Fig. 11) and tumours with no extension (Fig. 12), also with the tumours treated by conservative means. This similarity is not surprising, as small tumours tend to be spindle celled, posteriorly placed, with less extension, and are more likely to be the type treated conservatively.⁶

The dramatic rises in probability of death particularly seen for large tumours, those with epithelioid cells present, and those which have their sclera excessively invaded or perforated speak for themselves by comparison. The factors which may influence these graphs will be discussed below.

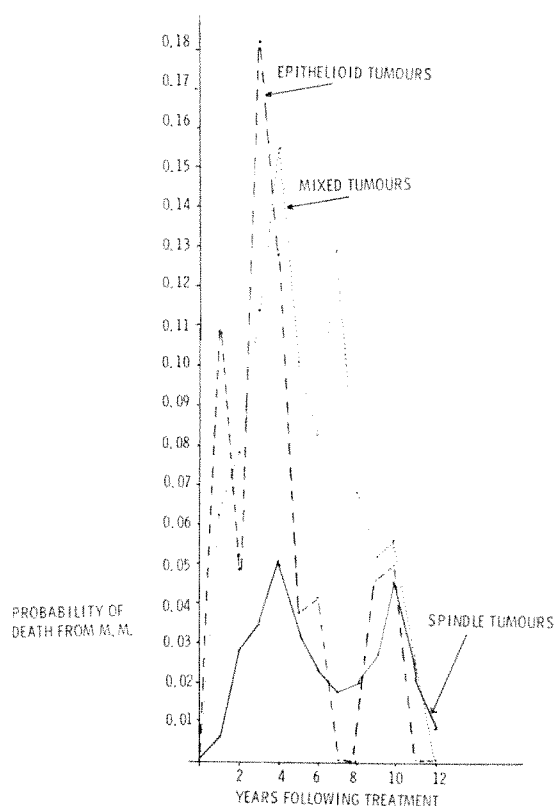


Fig. 11 Probability graph for death from choroidal malignant melanoma for cell type.

In order to assist further in the assessment of individual cases a discriminative analysis was carried out. Initially this was done in the linear manner suggested by McLean *et al.*² However, it was felt that cell type could not truly be assessed in such a manner as it implied that spindle cell tumours were necessarily of better prognosis than epithelioid tumours and mixed cell tumours somewhere in between. To give a more accurate picture the 3 cell types were assessed in this manner separately. Certain risk factors, notably pigment, were found to have a different influence in different cell type tumours. McLean *et al.*² felt that this finding in spindle cell tumours was due to misclassification of some of these tumours, which were really mixed cell type masked by pigment. However, if this were true, any prognostic value of pigmentation would be weakened in their analysis by the fact that mixed and spindle cell tumours were being considered together.

The results shown in Table 2 of the stepwise discriminant analysis suggest that the most important predictor for outcome is pigmentation in spindle

Table 2 Standardised discriminant function coefficients

Variable	Spindle (167)	Mixed (75)	Epithelioid (28)
LTD	-0.227	-0.517	-0.759
Pigmentation	-0.369	0.197	-0.155
Reticulin	-0.196	—	-0.389
AB location	0.236	—	—
PB location	—	—	0.232
Age	-0.223	-0.462	—
Sex	—	-0.389	-0.286
Scleral extension	-0.260	—	-0.162
Neurovascular channel extension	—	-0.261	-0.173
Bruch's membrane	-0.205	-0.215	—
Duration	—	0.267	0.336
Final Rao's V	96.34	74.17	103.56
Willis lambda	0.631	0.496	0.200
Canonical corr.	0.618	0.710	0.894

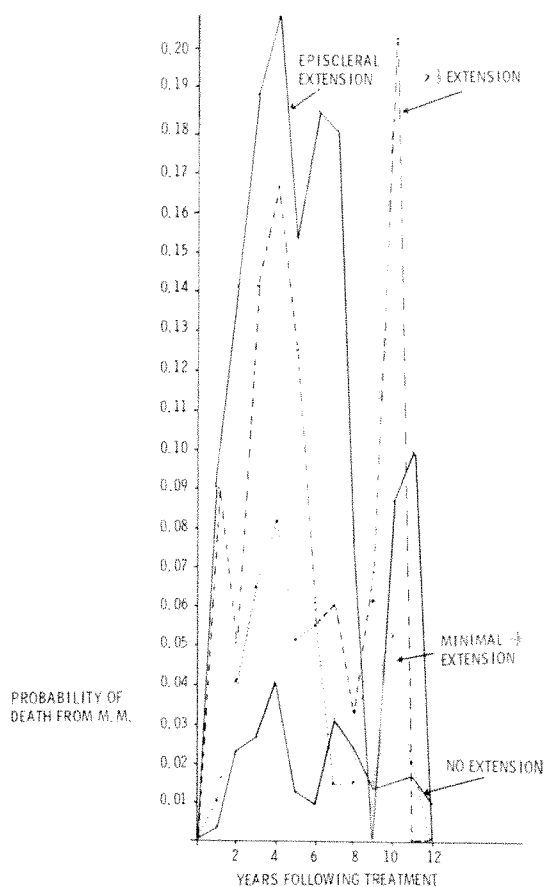


Fig. 12 Probability graph for death from choroidal malignant melanoma for scleral extension.

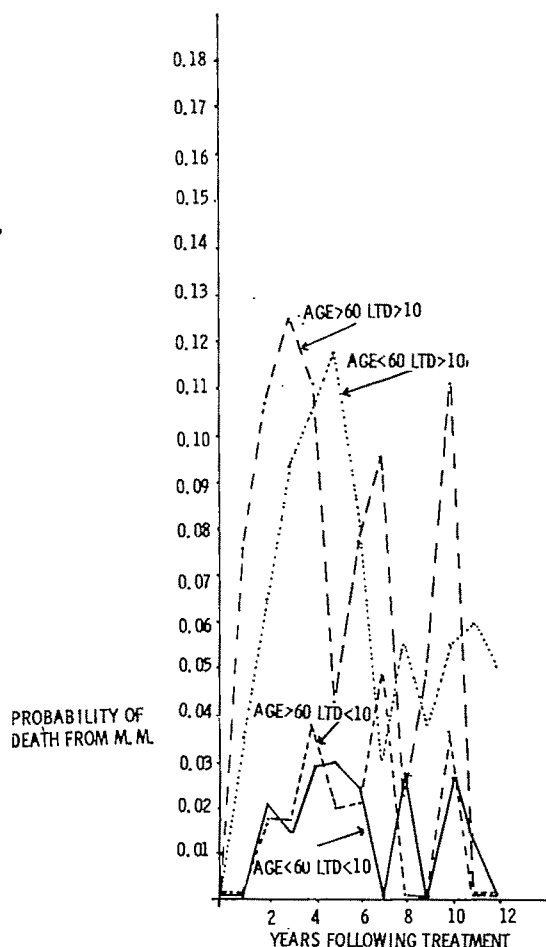


Fig. 13 Probability graph for death from choroidal malignant melanoma showing age in relation to size.

cell tumours and size in mixed and epithelioid tumours. It was hoped to be able to use this analysis for predicting outcome in individual cases, but results, even in this series, were disappointing with an accuracy of only 85%. As McLean *et al.*³ have suggested, one set of data from a retrospective survey does not necessarily give useful or accurate answers when applied to another set of data. Also as this analysis is entirely from enucleated patients, it is of no use unless this type of treatment is to be used.

Discussion

It was shown in the thesis⁴ on which this paper is based how as age increases tumours are more likely to have a longer history, be larger, more anteriorly placed, not be spindle celled, be more pigmented

particularly in females, have a greater degree of scleral extension, and a ruptured Bruch's membrane. However, it was also shown that large tumours per se are more often anterior, less likely to be spindle celled, have more pigment and scleral extension, and have a ruptured Bruch's membrane.

If the mortality patterns for the various factors are again reviewed it is obvious, for example, that as tumours get larger the survival worsens.

One similarity which should also be mentioned is between the 10-year survival in small enucleated tumours and those treated conservatively (81.4% for small tumours, 81.3% for conservatively treated tumours). This would suggest that enucleation need have little place in the treatment of such tumours as a primary procedure while good vision may be maintained; also that there is no greater likelihood of tumour spread than if the tumour is removed completely. As will be seen when the rates of mortality in other groups are considered in relation to enucleation, no such comforting picture may be said to exist in these other cases.

While reviewing the work of Paul *et al.*⁵ Zimmerman *et al.*³ noted certain points in the distribution of mortality, in relation to treatment by enucleation. This led these writers to postulate that this type of treatment might in fact be responsible for the peak in mortality which they demonstrated to occur 2 to 3 years after enucleation. The validity of this observation has been called into doubt by Siegel *et al.*,¹³ but the data in the present series and those of Benjamin *et al.*¹¹ and Jensen¹² show that such a pattern undoubtedly does exist. In fact as stated earlier 2 peaks are present.

Zimmerman and McLean⁴ have offered an explanation for the first mortality peak. The presence of such a peak was supposed to be found in many malignancies treated by surgery and also by irradiation.¹³ In fact, if one looks closely at Siegel *et al.*'s figures, the majority of the tumours which they cite either have no peak or have their highest mortality in the first post-treatment year, with death falling away in later years. Only in melanoma of the skin and breast carcinoma with regional involvement of the surgically treated cases and carcinoma of the cervix treated by irradiation is any similarity of pattern seen. We are not told whether the irradiation was administered by local insertion of radioactive materials in the patients with cervical carcinoma, which, if this were the case, would necessitate some local manipulation of the tumour.

The explanation of the second peak was at first hard to realise. It was possible that immunological factors were important, such that in those patients dying in the earlier peak they might be less able to cope with any outflow of metastatic cells from the

Table 3 Numbers and percentages of patients dying in 1st and 2nd 5-year postenucleation periods in each cell type group, excluding necrotic

	1st 5 years	2nd 5 years	Total patients dying
Spindle	46 (55.4%)	29 (34.9%)	83
Mixed	46 (63.9%)	19 (26.4%)	72
Epithelioid	19 (79.2%)	3 (12.5%)	24

Table 4 Percentage of patients with tumours of each cell type dying in each year after treatment

Year	Total	Spindle	Mixed	Epithelioid
0—	14	2 (14.3%)	7 (50.0%)	5 (35.7%)
1—	20	9 (45.0%)	8 (40.0%)	2 (10.0%)
2—	29	11 (37.9%)	11 (37.9%)	7 (24.2%)
3—	32	15 (46.9%)	13 (40.6%)	4 (12.5%)
4—	17	9 (52.9%)	7 (41.2%)	1 (5.5%)
5—	12	6 (50.0%)	5 (41.66%)	1 (8.33%)
6—	12	4 (33.3%)	7 (58.33%)	0
7—	7	4 (57.1%)	3 (42.9%)	0
8—	8	5 (62.5%)	2 (25.0%)	1 (12.5%)
9—10	12	8 (65.6%)	2 (18.0%)	1 (8.33%)

tumour at the time of enucleation than those patients dying in the later peak. In their case any foci of metastases may well be controlled immunologically for a time, but eventually this becomes inadequate and leads to death from the tumour. Another possibility was that metastases were slower growing, but this too may be under immunological control. It might have been shown that the tumours involved in the late mortality peak were of the predominantly spindle type and those in the early peak of the epithelioid or mixed type, and in fact there is a definite trend for this to occur (Tables 3 and 4). This suggests that the metastatic deaths occurring in the second peak tend to be due to slower growing tumours which may or may not be further immunologically controlled. There is also the possibility here that metastases are present prior to enucleation and because of their small size (maybe only a few cells) remain unsuspected, only growing to sufficient size to kill the patient either by the first or second peak in the mortality graph. However, it is strange that the incidence of pretreatment deaths from metastases is so rare even in the face of a wide variation in lengths of history. Further, that there should be 2 peaks related to the event of treatment adds weight to the evidence of tumour handling being involved as Turnbull *et al.* suggested^{14,15} in relation

to carcinoma of the large bowel and Fraunfelder *et al.*¹⁶ in relation to experiments on hamster eyes and pressure measurements during enucleation on humans.

As can be seen from the death rate curves for some of the different factors under study, certain types of tumours, i.e., large, anterior, nonspindle cell, etc., have marked peaks in comparison with small, posterior, spindle tumours. This also suggests that there is no direct relationship for this latter group to enucleation.

At present such views must still be speculation until there is a sufficient number of nonenucleated patients with similar tumours followed up for long periods, but I feel certain that the evidence which this paper has added to the idea of enucleation being a deleterious prognostic factor in certain tumours should not be overlooked. As suggested by Zimmerman and McLean,⁶ a pooling of all known cases not treated by enucleation on a world-wide basis and a prospective study by many centres are necessary before a definitive answer to this question may be achieved.

The secretarial services of Miss S. Cooper, Charing Cross Hospital, are gratefully acknowledged.

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Lymphoproliferative response as an index of cellular immunity in malignant melanoma of the uvea and its correlation with the histological features of the tumour

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SUMMARY Cell-mediated immunity and immune complexes were studied in 22 cases of malignant melanoma of the choroid and in 3 patients with iris melanoma. An attempt has been made for the first time to correlate the cell-mediated immunological changes with the histological features of the tumour and the extent of the disease. In most of the patients the lymphoblastic response to tuberculin and phytohaemagglutinin was within normal range, indicating that there is no obvious suppression of T lymphocyte-dependent immunity in intraocular melanoma. However, only about half the patients showed an increased lymphoproliferative response to their own tumour antigens or to pooled allogeneic melanoma extracts. The response to the latter was invariably weaker, suggesting that although melanoma antigens may show cross-reactivity there exists an element of individual specificity. As the transformation index was generally low (i.e., ≈ 3) it is tempting to conclude that uveal melanomas are either poorly immunogenic or that the immune system is insufficiently stimulated when the tumour is confined within the eye ball. The latter would seem more likely. Although the lymphocyte transformation test appears to be unreliable in the early diagnosis of intraocular melanoma, it promises to be useful in the prognosis of this tumour. The host immune system appears to be better stimulated if the tumour is large and contains a detectable proportion of epithelioid cells. Histochemical and ultrastructural examination of the lymphocytes infiltrating the tumour showed evidence of cytoplasmic activation, suggesting that these cells may be actively engaged in tumour homeostasis. With one exception Clq-binding immune complexes were not raised in the blood of the patients examined so that tumour-enhancement (through this mechanism at least) may not be an important feature in the natural history of intraocular melanoma.

Interest in the natural history of malignant melanoma of the uvea and in the existence of a host defence mechanism has been stimulated by the observation that uveal melanomas may remain localised for long periods—over 30 years in 1 case.¹ It is also known that malignant melanomas of the iris rarely metastasise,^{2,3} while some intraocular melanomas may even undergo spontaneous regression.^{4,5} In an attempt to explain this puzzling behaviour of some uveal melanomas several hypotheses have been put forward, such as the effects of the host environment,⁶ defensive substances,⁷ bio-

chemical barriers,⁸ and specific immune mechanisms.⁹

Although much of the antigenicity of tumour extracts is attributable to components shared with non-neoplastic cells, there are also antigens which are peculiar to tumour cells in general and uveal melanoma in particular.⁹ These tumour-associated antigens are conveniently divided into 2 categories: those associated with the surface membrane and those linked with the intracytoplasmic contents. The surface membrane antigens can initiate a transplantation rejection process, so that these antigens have also been called tumour-specific transplantation antigens. Both surface and intracytoplasmic tumour-associated antigens have been

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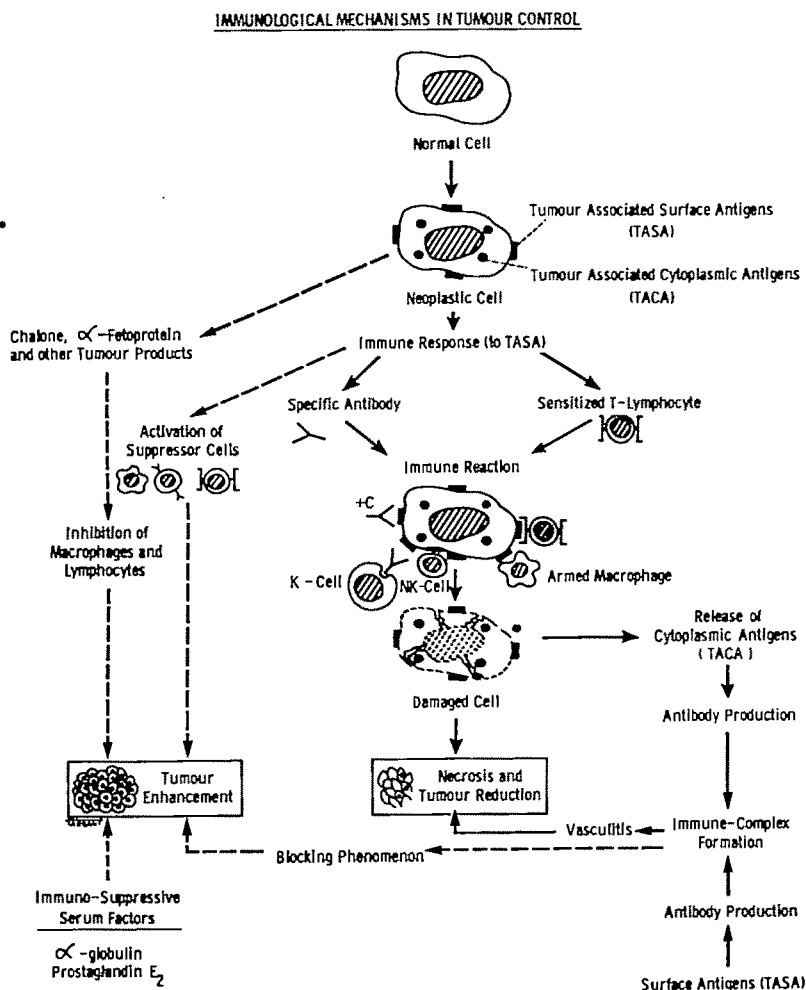


Fig. 1 Tumour-associated surface antigens (TASA) lead to both humoral and cellular immune responses. An antibody-mediated reaction on the surface of a neoplastic cell may lead to direct cell damage either through the lytic activity of the complement or through a K cell and macrophage-related response. Activated T lymphocytes are cytotoxic to cancer cells. Tumour necrosis is accentuated by the release of inflammatory lymphokines, some of which are known to activate and arm macrophages to destroy neoplastic cells. The release of tumour-associated cytoplasmic antigen (TACA) from damaged cells further stimulates the immune system and leads to the formation of immune complexes which either produce local inflammatory reaction and tumour necrosis or lead to the blockade of T cell receptors and tumour enhancement. This tumour enhancement may also result from several other humoral factors and various tumour cell products.

described in malignant melanoma of the choroid,^{9, 10} and it would seem that, whereas there is a considerable sharing of intracytoplasmic tumour antigens between one uveal melanoma and another, most surface antigens are peculiar to an individual tumour. It is possible, however, that melanomas of the uvea may resemble those of the skin in having 2 additional types of surface antigens: one being specific to melanoma cells but common to a number of individual tumours (histotype-specific) and the other shared with neoplastic and non-neoplastic tissues in a number of species.¹¹⁻¹³ Since antibodies do not penetrate intact cell membranes, the role of cytoplasmic antigens in stimulating an effective host defence mechanism is questionable. Conversely antibodies to surface membrane antigens appear to be cytotoxic to uveal melanoma cells in short-term tissue culture studies¹⁴ and are more likely to be

involved in host immunity. It is now accepted that, as with graft rejection, the control of tumour growth is mainly executed by T lymphocytes, which differ from antibody in not requiring complement to exert cytotoxic activity and in being able to penetrate solid tissues (Fig. 1). Delayed cutaneous hypersensitivity to soluble extracts of melanoma cells have been studied in patients with intraocular malignant melanoma.¹⁵ Although the majority of the patients tested showed a positive skin reaction to the test antigen, the reaction was negative in a significant proportion of histologically confirmed patients, and false positive results were obtained in about 20% of patients with benign or non-neoplastic intraocular lesions.

Although the skin test appears to correlate well with cellular immunity, particularly against infective organisms, the expression of skin reactivity itself

depends not only on the infiltrating T lymphocyte but also on the vasculature and the microanatomy of the test site and the capacity of an individual to mount a nonspecific inflammatory response following injury.¹⁶ To overcome these in-vivo limitations it has been suggested that in-vitro tests should be carried out. Manor and co-workers¹⁷ therefore studied direct (i.e., 1-stage) macrophage migration inhibition tests in patients with uveal melanoma in which a crude extract obtained from 4 allogeneic (i.e., homologous) intraocular melanomas were used as a source of antigen. This test seemed to provide good discrimination between malignant and benign pigmented tumours. However, its specificity as an indicator of cellular immunity is now being questioned because tissue extracts may either be cytotoxic to leucocytes and cause nonspecific migration inhibition or contain other substances such as antibodies which may alter the cell membrane of these cells and inhibit their movement.¹⁸ It has been suggested, therefore, that indirect (i.e., 2-stage) migration inhibition assays (in which the macrophages are incubated with the supernate obtained from a culture of patients' lymphocytes incubated separately with the test antigen) should provide more reliable results.¹⁹

Cell-mediated immunity in malignant tumours including those of the uvea has also been studied by a macrophage electrophoretic mobility (MEM) test.^{20,21} The technique is based on the concept that lymphocytes from patients with cancer are sensitised to a basic protein present in human brain and cancer cells. When incubated with this antigen, the sensitised lymphocytes release a macrophage-slowing factor which can be detected by its effect on the electrophoretic mobility of guinea-pig macrophages. This technique differs from the conventional macrophage migration inhibition test in that in the MEM test it is the passive movement rather than the active migration which is grossly affected. Although the validity of this in-vitro blood test has been confirmed,^{22,23} several other workers, including ourselves, have been unable to do so and found that technical limitations which make standardisation difficult render the test of little value.^{21,24-26}

Malignant melanoma of the uvea can pose diagnostic problems despite the development of such sophisticated techniques as fluorescein angiography, the ³²P test, and ultrasonography. A mistaken diagnosis of malignancy is more common in small tumours of the uvea,²⁷ and the incidence of unnecessary enucleation may be as high as 20%.²⁸⁻³⁰ Because of this there is a considerable incentive to develop a reliable technique for the preoperative diagnosis of malignant melanoma.

The serological diagnosis of an intraocular

malignant melanoma appears to be difficult because of the presence of ostensible antimelanoma antibodies in patients with non-neoplastic eye disease,^{12,13} and it seems unlikely that antibodies alone are responsible for tumour homeostasis. We decided, therefore, to investigate other parameters of host immunity to tumours. Since skin tests, leucocyte migration inhibition tests, and macrophage electrophoretic mobility tests have been carried out with variable success in the diagnosis of intraocular malignancy, and it has been reported that the lymphocyte transformation test using radioactive thymidine is easy to quantitate and correlates well with the extent of the disease in relation to malignant melanoma of the skin,³¹ we have attempted to evaluate the usefulness of the latter test as an immunodiagnostic procedure.

Methods and materials

Fresh tumour cells obtained from enucleated eyes were homogenised in sterile phosphate-buffered saline (pH 7.4) with a pestle and mortar and then transferred to an electrical blender for further homogenisation. The suspension was centrifuged at 2000 *g* for 10 minutes to remove cellular debris, nuclei, and melanin pigment. It was then dialysed against phosphate-buffered saline (pH 7.4) for 24 hours at 4°C and stored in liquid nitrogen until used. Antigenic extracts were also prepared using hypertonic potassium chloride solution as originally described by Meltzer *et al.*³² The cell suspension obtained from minced tumour material was suspended in 20 ml of 3 M KCl (pH 7.4) and left at 4°C for 24 hours with frequent shaking. The suspension was centrifuged at 40 000 *g* for 60 minutes and the supernate was dialysed for 16 hours against phosphate-buffered saline (pH 7.4). The dialysed material was centrifuged again at 40 000 *g* for 15 minutes. The supernatant was concentrated by using Lyphogel and sterilised by passing the solution through a Millipore filter (0.22 µm). The protein concentration was estimated by a modified Lowry method.³³

LYMPHOCYTE CULTURE

Blood was collected before enucleation in preservative-free heparin (20 units per ml) and lymphocytes were separated by a density-gradient technique using a Ficoll-Hypaque preparation (Pharmacia). After the viability of lymphocytes had been tested by the trypan blue technique they were cultured in medium 199, each millilitre of which contained 200 units of penicillin and 100 µg of streptomycin. The medium was enriched immediately before use by

the addition of the patient's own serum (1:10) and freshly prepared glutamine (2 mmol/ml). The test was carried out in Sterilin tubes in a gaseous phase of 5% carbon dioxide in air; 10^6 lymphocytes suspended in 1 ml of the enriched nutrient medium were put in each tube. In an initial study various concentrations of the crude preparation as well as potassium chloride extracted antigens were used to obtain a dose-response curve. Suitable amounts of both autochthonous (i.e., autologous) and pooled allogeneic (i.e., homologous) antigen preparations were added separately to the various culture tubes 24 hours after the initial incubation of the lymphocytes, during which time the suppressor lymphocytes appear to become less effective and do not grossly interfere with the lymphoproliferative response of antigen-sensitive lymphocytes (Brostoff, personal communication). In order to study the state of cellular immunity in general, the lymphocytes from patients with malignant melanoma of the uvea were also cultured with various concentrations of specific and non-specific mitogens such as purified protein derivative (PPD) and phytohaemagglutinin (PHA). Controls to exclude a possible mitogenic effect of normal human choroid were set up and the various tests were carried out in duplicate.

In order to study the specificity of this test melanoma antigens were also added to the lymphocyte from healthy individuals, from patients with nonmalignant eye diseases, including disciform macular degeneration, sympathetic ophthalmitis, melanocytoma (magnocellular naevus) of the ciliary body, and naevus of the iris, and also from a case of carcinoma of lung with metastases in the choroid. 2 μ Ci of tritiated thymidine (specific activity 20 Ci/mmol) were added to each control and the experimental tubes on the 6th day of the experiment, and incubated for a further period of 16 hours. The lymphocytes were then harvested by centrifugation; the supernatant was deep frozen and studied later for evidence of lymphokine production. The lymphocytes were resuspended in phosphate-buffered saline and passed through a specially designed funnel containing fibreglass filter paper. They were washed with 5 ml of 10% trichloroacetic acid and 20 ml methanol. The filter paper was transferred to scintillation vials and dried in an oven at 37°C for 3 hours; 10 ml of toluene-based scintillation fluid was added to each vial, and the lymphoproliferative response was measured in terms of ^{3} H thymidine uptake (for DNA synthesis) in a Packard tricarb liquid-scintillation counter. The disintegration was expressed in counts per minute. To obtain the transformation index the count in the vial containing antigen-treated cells was divided by the radioactivity in that containing unstimulated cells.

INDIRECT MACROPHAGE MIGRATION INHIBITION TEST

Macrophages were obtained from adult male Hartley guinea-pigs 6 days after the injection of 25 ml of sterile liquid paraffin into the peritoneum. Heparinised Hanks's fluid was injected into the peritoneal cavity, and the macrophage-rich suspension was aspirated with a 20 ml syringe attached to a perforated polypropylene tube, care being taken not to traumatise the tissues. The cell suspension was passed through a separating funnel, spun at 250 g for 10 minutes, and resuspended in medium 199. The concentration was adjusted to 8×10^6 cells per millilitre of the medium, which was enriched with normal guinea-pig serum. The indirect (i.e., 2-stage) inhibition studies were carried out in specially designed Sterilin chambers. During the study it was found that Plasticine used to seal the capillary tubes produced nonspecific inhibition of macrophages, and therefore a small amount of sterile silicon gel was introduced into the capillary tube to separate the macrophage column from the Plasticine. The cells were incubated in the supernatant obtained from the unstimulated culture, and the area of migration was compared with those in supernatants from antigen-treated cells. Supernatant from antigen-treated lymphocyte cultures from healthy individuals was also used in a separate study to exclude any nonspecific inhibitory effect of melanoma extract.

Migration inhibition of more than 25% giving an index of less than 0.75, was regarded as abnormal for the present study.

IMMUNE-COMPLEX ESTIMATION

It has been shown that a tumour may sometimes show a marked increase in size in the presence of an apparent immune response. This is known as tumour enhancement, and it is now considered to be due to blocking of antigen-specific receptors on T lymphocytes by free tumour antigens or antigen-antibody complexes.²⁴ It is possible, therefore, that the in-vitro lymphoproliferative responses to tumour antigens may also be modified by the presence of antigen-antibody aggregates in the patients' serum.²⁵ Sera from melanoma patients was investigated, therefore, for the presence of soluble immune-complexes using an ^{125} I-C1q binding assay. C1q was isolated from normal human serum and radioiodinated by the lactoperoxidase method. Fixed amounts of radiolabelled C1q were added to the test serum, and the complexes were precipitated with 3% (w/v) polyethylene glycol (PEG). The mixture was centrifuged at 1500 g for 20 minutes at 4°C, the supernatant was discarded, and the radioactivity of the precipitate was measured. Results were expressed

sed as a percentage of ^{125}I -C1q precipitate relative to the radioactivity in the control tube in which normal serum containing the same amount of radiolabelled C1q is precipitated with 20% trichloroacetic acid (TCA). Blood from 50 healthy adults and 52 cases with various eye diseases was also tested for immune complexes, and the data obtained were used for comparison and statistical analysis. In the present study only those samples that showed ^{125}I -C1q binding of 12% or over were regarded as abnormal and were considered to contain raised levels of immune complexes.

HISTOLOGICAL EXAMINATION

After removal of part of the tumour for immunological studies the enucleated eyes were fixed in buffered formol saline, and paraffin sections were stained with haematoxylin and eosin and methyl green and pyronine Y for histological examination. The sections were bleached in cases where the pigment content made it difficult to assess the cell type. The largest diameter of the tumour in contact with the sclera was measured in millimetres. The sections were also examined for evidence of necrosis, lymphocytic infiltration, immunoblastic transformation (i.e., pyroninophilia), and extraocular extension. A portion of the tumour was first fixed in glutaraldehyde and then in osmium tetroxide and blocked in Araldite for electron microscopical examination. The sections were stained with lead citrate and uranyl acetate and examined with a JOEL 100C transmission electron microscope. Statistical analysis of the immunological investigations was carried out by Fisher's exact test.

Results

A transformation index of 2 or more was regarded as evidence of sensitisation to tumour antigens. The lymphocyte transformation test using autochthonous (i.e., autologous) tumour extract was performed in only 19 of the 22 cases of malignant melanoma of the choroid because enucleation was not undertaken in the other 3 cases. An increased lymphoproliferative response was seen in 10 cases (Table 1). The response to allogeneic tumour antigen, however, was weaker than that incurred by autologous tumour extract. In general, the response to KCl extracted antigen was marginally stronger than that to the crude antigen preparation. There was also a wide variation in the response to PPD and PHA, but with the exception of 5 cases (see Tables 1 and 3) the transformation index was generally within the normal range (that is, ≥ 12 for PHA).

Generally it was found that patients who showed

marked reactivity towards PPD and PHA also showed a response to tumour antigens. It can be argued that a generally low uptake of radioactivity in our experiment was due to the fact that ^3H -thymidine of a high specific activity (20 Ci/mmol) was used, since this might have damaged some of the lymphocytes. We have used, however, the same isotope with a low specific activity, i.e., 2 Ci/mmol, in 6 cases without any marked changes in the lymphoproliferative response. The lymphoproliferative response to normal human choroidal extract was studied in only 9 patients, and the transformation index in these cases was always < 2 . This is in keeping with the previous report in which it was shown that antimelanoma antibodies do not cross-react with normal choroid.³⁶

The lymphocyte transformation test was carried out in only 3 cases of malignant melanoma of the iris; autochthonous (autologous) tumour antigen was used in 2 patients, and a high thymidine uptake was present in both cases (Table 2). The reactivity towards allogeneic tumour was weaker, and in only 1 case was there an appreciable increase in the DNA synthesis. The response to PHA was within the normal range in 2 of the 3 cases examined.

The lymphoproliferative response to allogeneic melanoma extract was minimal or negligible in healthy controls as well as in patients with clinically benign lesions, secondary carcinoma of the choroid, and in non-neoplastic eye disease. The response to PHA in most of these cases was normal (Table 3). The statistical analysis of the lymphoproliferative response and its correlation with various histological parameters are summarised in Table 4.

In cases where the lymphocyte transformation test was positive (Table 1) it was found that the tumour was generally large ($P < 0.001$), the largest diameter in contact with the sclera being 12 mm or over, though there was 1 exception in which a tumour with a diameter of 15 mm showed a transformation index with autochthonous tumour extract of less than 2. In the case of iris melanoma a positive response was associated with a diffuse infiltrating tumour.

Extraocular extension was evident in 6 cases of malignant melanoma of the choroid and in 1 patient with iris melanoma. The lymphocyte transformation test was positive in all of them ($P < 0.001$).

In only 1 case was the tumour of epithelioid cell type, 8 cases were of mixed variety, and the rest were composed almost exclusively of spindle cells. The lymphoproliferative response was increased only in patients with a mixed-cell type of melanoma ($P < 0.001$).

Pigmentation was heavy in 4 cases, moderate in another 6, and light in the rest. There was no corre-

Table 1 Cellular immunity in malignant melanoma of the choroid and its correlation with the biological behaviour of the tumour

No.	Sex	Histological features				Cellular immunity								
		Largest diameter of the tumour in contact with the sclera	Cell type	Pigmentation	Necrosis	Hydropic degeneration	Mitosis	Lymphocytic infiltration	Extra-ocular extension	Transformation Index				
										Autoclithorous (autologous) tumour extract	Allogeneic (homologous) tumour extract	PPD	PHA	Migration inhibition test
1	Male	13 mm	Mixed	Heavy	++	-	++	+	+	2.0	•	•	42	-
2	Male	15 mm	Mixed	Heavy	+	-	++	+	+	2.0	2	•	30	+
3	Female	13 mm	Epithelioid	Light	+	-	++	++	+	2.2	2.0	•	40	•
4	Male	12 mm	Mixed	Light	-	+	-	+	-	3.4	3.0	•	155	•
5	Male	12 mm	Mixed	Light	-	-	-	+	-	2.2	2.0	7	150	•
6	Male	14 mm	Mixed	Heavy	+++	-	-	±	-	2.0	2.0	4	41	•
7	Female	12 mm	Spindle	Light	-	+	++	+	+	2.3	2.0	10	90	•
8	Male	14 mm	Mixed	Light	+	-	++	+	+	2.0	2.0	3	49	•
9	Male	13 mm	Spindle	Light	+	-	+	+	-	3.0	2	•	53	•
10	Female	15 mm	Mixed	Moderate	+++	-	-	+	+	6.2	2.5	•	130	•
11	Female	7 mm	Spindle	Moderate	-	-	-	-	-	0.8	0.7	•	19	•
12	Male	9 mm	Spindle	Light	-	+	+	±	-	0.9	0.7	•	27	•
13	Male	6 mm	Spindle	Moderate	-	-	-	-	-	0.8	0.8	•	7	•
14	Male	15 mm	Spindle	Moderate	-	-	+	-	-	0.9	0.8	•	7	•
15	Male	5 mm	Spindle	Moderate	-	-	-	-	-	1.2	1.0	•	47	•
16	Male	7 mm	Spindle	Light	-	-	+	+	-	1.2	1.0	•	47	•
17	Male	11 mm	Spindle	Moderate	-	-	+	-	-	0.9	0.8	•	11	•
18	Female	10 mm	Spindle	Light	-	-	+	-	-	0.8	0.8	1	8	•
19	Male	10 mm	Spindle	Light	-	-	-	-	-	0.9	0.8	•	12	•
20	Male				No histology					•	1.6	•	42	-
21	Female				No histology					•	0.8	•	20	-
22	Female				No histology					•	0.8	•	10	•

*Not done.

•Not done.

Table 2 Cellular immunity in malignant melanoma of the iris and its correlation with the histological behaviour of the tumour

No.	Sex	Histological features				Cellular immunity								
		Nature of growth	Cell type	Pigmentation	Necrosis	Hydropic degeneration	Mitosis	Lymphocytic infiltration	Extra-ocular extension	Transformation index				
										* Autoclithorax (autologous) tumour extract	Allogeneic (homologous) tumour extract	PPD	PHA	
1	Male	Diffuse infiltrative	Spindle	Light	-	-	-	+	+	2.4	2	•	43.7	+
2	Male	Diffuse infiltrative	Mixed	Heavy	-	-	-	-	-	2	1.8	6	52	•
3	Female				No histology						0.4	1.4	6	•

Not done

•Not done.

Table 3 *Lymphoproliferative response to melanoma antigens in the control group*

No.	Sex	Nature of lesion	Cellular immunity	
			Transformation index	
			Allogeneic (homologous) tumour extract	PHA
1	Male	Disciform macular degeneration	0.96	50
2	Female	Sympathetic ophthalmitis	1.0	34
3	Male	Lepromatous iritis	1.0	27
4	Male	*Melanocytoma of the CB (magnocellular naevus)	0.93	20
5	Male	Iris naevus	0.8	13
6	Male	*Lung carcinoma with choroidal metastases	0.9	34
7	Male	*†Metastatic adenocarcinoma (choroidal)	0.84	4.7
8	Male	Healthy control	1.1	28
9	Male	Healthy control	1	39
10	Male	Healthy control	1	60
11	Male	Healthy control	1	47
12	Male	Healthy control	1.2	40

*Histologically confirmed. †A state of generalised immunosuppression cannot be ruled out. CB = ciliary body.

lation between the degree of pigmentation and the lymphoproliferative response.

Distinct apoptosis and coagulative necrosis were evident in 6 cases and absent in the remaining 15 cases. The tumour-specific immune response appeared to correlate well with the extent of necrosis ($P < 0.001$).

Lymphocytic infiltration (Fig. 2) was extensive in 2 cases, prominent in 8 cases, and occasional in 2 cases. The remaining 9 cases did not show any round cell infiltration in the sections examined. Methyl green pyronine Y staining showed the presence of occasional immunoblasts among the infiltrating lymphocytes, thus providing direct evidence of in-vivo activation of these cells. Electron microscopic examination complemented this finding and revealed the presence of lymphocytes with well developed rough endoplasmic reticulum and prominent mitochondria (Fig. 3).

Mitotic activity was markedly increased in 3 cases, all of which had a positive lymphoproliferative response. A moderate to low activity was seen in 7 patients, and the test was positive in only 2 patients. The mitotic activity does not appear to correlate with the degree of blastic response.

^{125}I -C1q binding assay was carried out in 22 cases of malignant melanoma of the choroid and 3 cases of iris melanoma and the results were com-

Table 4 *Tumour-specific immunity in malignant melanoma of the uvea: analysis of significance*

Characteristics	No. tested	No. positive	No. negative	Significance
Control (C)	12	0	12	
Diameter	≤ 10 mm (D1)	7	0	D1 vs C NS
	> 10 mm (D2)	14	12	D2 vs C $P < 0.001$ D2 vs D1 $P < 0.001$
Cell type	Spindle (TS)	12	3	TS vs C NS
	Mixed (TM)	9	9	TM vs C $P < 0.001$ TM vs TS $P < 0.005$
Necrosis	Present (N1)	6	6	N1 vs C $P < 0.001$
	Absent (N0)	15	5	N0 vs C NS N1 vs N0 $P < 0.05$
Lymphocytic infiltration	Present (L1)	13	11	L1 vs C $P < 0.001$
	Absent (L0)	8	1	L0 vs C NS L1 vs L0 $P < 0.01$
Mitosis	Present (M1)	10	5	M1 vs C $P < 0.05$
	Absent (M0)	11	7	M0 vs C $P < 0.05$ M1 vs M0 NS
Extraocular extension	Present (X1)	7	7	X1 vs C $P < 0.001$
	Absent (X0)	14	5	X0 vs C NS X1 vs X0 $P < 0.05$

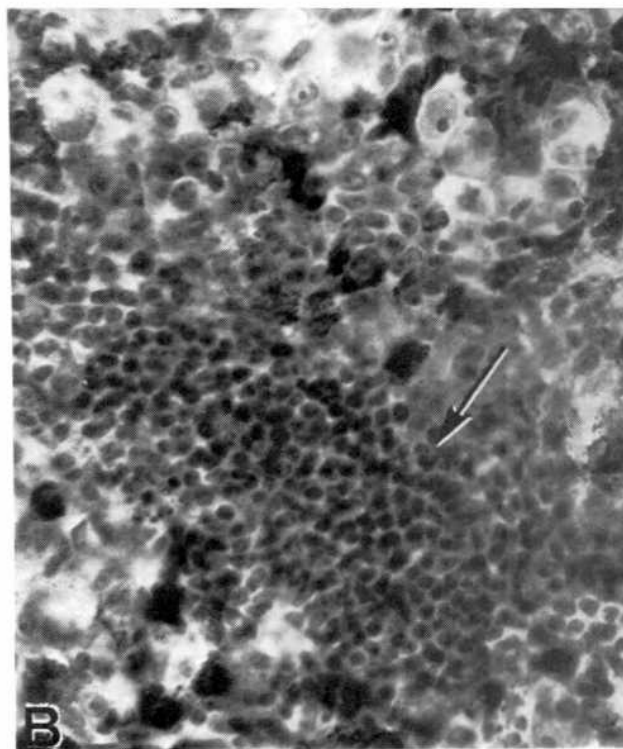
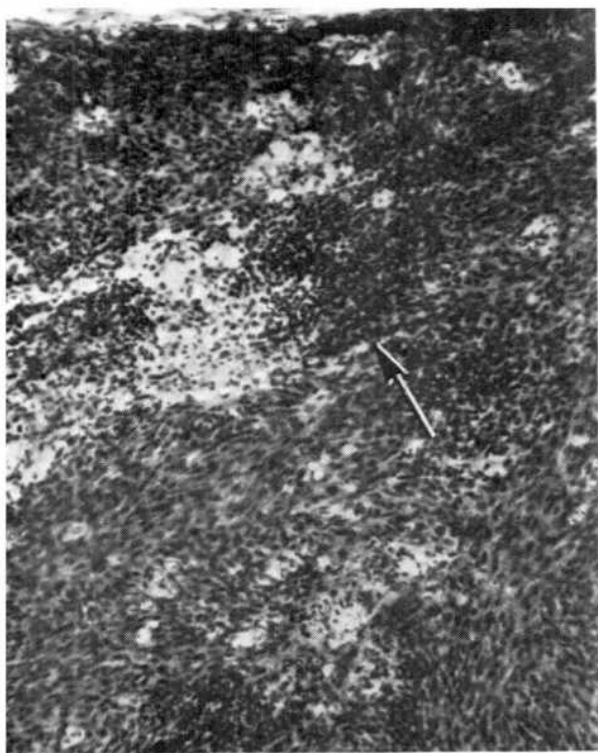


Fig. 2 Section of a malignant melanoma of the choroid showing lymphocytic infiltration, A: Spindle cell melanoma, (H and E, $\times 185$), B: Mixed cell melanoma, (H and E, $\times 590$).

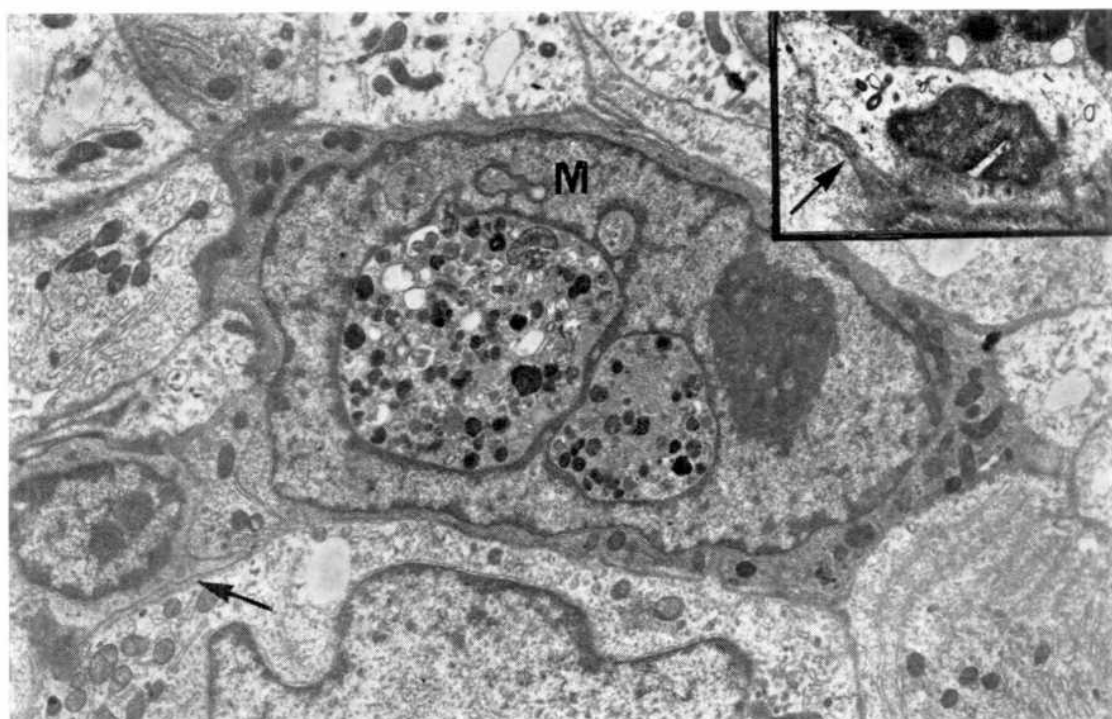


Fig. 3 Transmission electron micrograph showing a melanoma cell (M) with an intranuclear cytoplasmic inclusion. The adjacent cell is a lymphocyte ($\times 10\,670$). The inset shows an activated lymphocyte with a cleaved nucleus and abundant cytoplasm containing ribosomes ($\times 6400$).

Table 5 Immune complexes in the blood from patients with malignant melanoma of the uvea (^{125}I C1q binding assay)

Nature of the lesion		No. tested	No. positive (binding $\geq 12\%$)
Control	Healthy adults	50	—
	Degenerative eye disease	50	—
	Melanocytoma ciliary body	1	1
	Benign iris naevus	1	—
Malignant melanoma choroid	+ve LTT	10	1
	-ve LTT	12	—
Malignant melanoma iris	+ve LTT	2	—
	-ve LTT	1	—

LTT = Lymphocyte transformation test (see Tables 1 and 2).

pared with those in the control group. With 1 exception the serum C1q binding activity in melanoma patients was less than 12%, and therefore the levels were regarded as lying within the normal range (Table 5).

The indirect macrophage migration inhibition test was carried out in only 4 cases of malignant melanoma of the choroid and in 1 patient with iris melanoma. The test was positive in 1 patient with choroidal melanoma and in the patient with an iris melanoma (see Tables 1 and 2).

Discussion

Both humoral and cellular immunity have been demonstrated in a variety of tumours in man, including malignant melanoma of the skin. It is generally considered, however, that cell-mediated immunity is primarily responsible for tumour rejection in experimental animals, and several reports indicate that a similar mechanism may operate in human neoplasms.³⁷

The antigens that elicit this type of reaction appear to be located on the cell membrane and behave as tumour-specific transplantation-like antigens. Since in our experiments, apart from 3 MKC1 solubilised membrane proteins, we also used homogenised tumour extract, it can be argued that the stimulatory antigens were of both membranous and cytoplasmic origin. It is possible, therefore, that the responding lymphocytes in these 2 experiments belong to separate subsets.

As humoral immunity has already been demonstrated in malignant melanoma of the choroid^{9,38} the finding of T cell reactivity to tumour extract raises the question of their respective roles in the host's defence mechanism against such tumours.

Although it is generally agreed that T lymphocyte mediated immunity is of more significance in tumour control, it is not certain whether the lymphocytes which show increased DNA synthesis (as seen in the present study) represent cytotoxic T cells or helper T cells which co-operate with B lymphocytes in the production of tumour-specific antibodies.

The delayed hypersensitivity skin test remains one of the simplest means currently available for the clinical assessment of the status of cellular immunity in man. Melanoma-associated antigens from allogeneic choroidal tumour extract have been used for the diagnosis of intraocular melanoma.¹⁵ Whereas 90% of the patients with histologically confirmed intraocular melanoma gave a positive skin response, about 20% of patients with nonmalignant diseases also showed a positive reactivity towards melanoma extract. The authors argue that the false positive results may have been due to contamination of the antigenic preparations with normal tissue constituents against which the patients in the control group had been sensitised, but this explanation is equally applicable to those cases which the authors regarded as true positives.

It is now accepted that the skin test as a correlate of cellular immunity has several limitations. Under certain circumstances the delayed cutaneous hypersensitivity may actually be depressed at a time when there is an intense cell-mediated reaction to the same antigen elsewhere in the body. It is known, for example, that in experimental allergic orchitis there may be a depression in skin test reactivity at a time when the test is diffusely infiltrated by lymphocytes. This depression in skin reactivity is evident even when such non-cross-reacting antigen as tuberculin is used.³⁹

It is now well documented that a positive delayed skin test is dependent not only on a specific immunological reaction but also on the patient's ability to mount a nonspecific inflammatory response.¹⁶ The interpretation of abnormal results, therefore, may sometimes be difficult. Furthermore, to determine whether or not the patient has T cell mediated immunity to the test antigen, the individual should develop a skin reaction consisting of at least 5 mm or more of induration at the test site 48 hours after the intradermal injection of the antigen (as is the case in Char's study on ocular melanoma). It should be noted, however, that such a reaction, especially if it is not strong, may not always represent a cell-mediated hypersensitivity because it could very well be a remnant of a previous Arthus-type reaction. In addition, the induration which is the hallmark of delayed cutaneous allergy is in fact dependent on vascular leakage and deposition of

fibrin,¹⁰ which may be defective in some individuals and in those on anticoagulant therapy. Skin tests are often difficult to quantitate, and often it is not easy to produce an absolutely sterile tumour extract for injection in man, especially with respect to possible contamination with hepatitis B virus. Furthermore, it may be impossible to exclude a carcinogenic effect of tumour extracts when injected into healthy human volunteers used as controls.

The alternatives to skin testing are macrophage and leucocyte migration inhibition and lymphocyte transformation tests. As mentioned earlier, positive inhibition tests have been reported in choroidal malignant melanoma, indicating that a degree of cellular immunity is present in these patients. The macrophage migration inhibition test (MMT) in which guinea-pig peritoneal macrophages are used may be subject to variation either due to nonspecific reaction of the proteins in tumour extract with the macrophages directly or through the activation of xenogeneic (heterologous) lymphocytes which often contaminate such preparations.

In addition it is well known that some antigens may produce 'toxic' migration inhibition by inhibiting both sensitised and nonsensitised cells.¹¹ It has also been shown that migration inhibition tests are most successful when particulate antigens are used. Soluble antigens may fail to cause inhibition of migration even when other tests give a positive cell-mediated reaction.¹¹ Negative results should therefore be treated with caution. Migration inhibition studies involving choroidal melanomas should be assessed against this background.

The lymphocyte transformation test (LTT) appears to have an enormous range of application. Whereas the skin test assays predominantly the effector limb of delayed hypersensitivity, which is mediated through a subset of T lymphocytes known as (TDH), the LTT can detect the activity not only of these cells but also of the helper T cells (TH), which modulate the activity of the antibody producing B lymphocytes. Suppressor T lymphocytes (TS) are also activated during an in-vitro lymphoproliferative response.

Although there are a variety of in-vitro tests to evaluate cell-mediated immunity, the LTT provides a simple and relatively more reproducible and easily quantifiable method. But this technique also has its own limitations. A nonspecific lymphoproliferative response can be induced by the constituents of the culture media as well as the contents of various xenogeneic (heterologous) and allogeneic (homologous) serum products; excessively vigorous handling of lymphocytes may also stimulate T cells. We have therefore used only autologous serum in these experiments. Since the uptake of radioactive thymi-

dine increases with the duration of incubation because of exponential cell growth, proper statistical assessment is difficult unless data are normalised, i.e., expressed in such a way that a normal distribution is obtained again. Although the technique of expressing the result as transformation indices rather than absolute counts normalises the data to some extent, it is assumed that the degree of reactivity in the antigen-treated and nontreated culture tubes will be affected by the various variables in the same way and will remain proportional. Unpreventable preincubation stimulation of the lymphocytes may, however, at the same time elevate the response in the control tube and interfere with the reactivity of lymphocytes with the test antigen in the experimental tube. For example, the patient may be allergic to antibiotics used in the culture serum. Fortunately, however, there was no reason to suspect the latter complication in any of the cases in the present study.

Since the lymphoproliferative responses can involve both T and B lymphocytes, the LTT would appear to reflect a wider spectrum of host immunity than either the skin test or the migration inhibition test, these tests depending almost entirely on the reactivity of T lymphocytes.

The lymphoproliferative response to autochthonous and allogeneic extract of malignant melanoma of the choroid were studied in 22 cases of choroidal malignant melanoma. An increased DNA synthesis was demonstrable in 12 of the 21 histologically confirmed cases; in the remaining 4 cases, in which the diagnosis was based on clinical evidence alone, the lymphoproliferative response was negative when using allogeneic tumour extract.

A positive lymphoblastic response to autochthonous tumour extract was also associated with some reactivity towards allogeneic tumour extracts, but the thymidine uptake was comparatively lower in the latter series. This suggests that the response was due to antigens which, although showing features of cross-reactivity, have some element of individual specificity. Whereas it is possible that the response to allogeneic tumour extract was due to histoincompatibility, it would seem unlikely, because the thymidine uptake following treatment with allogeneic tumour extract was never higher than uptake by the lymphocytes when challenged with autochthonous (autologous) extract.

The lymphoblastic response to phytohaemagglutinin (PHA) was normal except in 5 cases in which the response to autochthonous or allogeneic tumour extract was not only poor but showed evidence of a degree of inhibition rather than proliferation. It is tempting to speculate that this was due to the presence of specific inhibitors of mitosis (i.e.,

chalones¹²) in the tumour extract, as similar compounds are known to be present in malignant plasmacytoma.¹³ It has also been suggested that autologous serum from cancer patients may have an inhibitory effect on in-vitro lymphoproliferative responses.¹⁴ While this could account for the relatively low transformation index in some of our patients,¹⁵ this nonspecific inhibitory influence which is either due to α -macroglobulin (Kamrin-Mowbray factor) or to nonspecific binding of antigen to other plasma constituents is usually seen at a serum concentration much higher than that used in the present study.¹⁶ It has not been possible, however, to exclude the possible inhibitory role of α -fetoprotein in these cases.¹⁷ Furthermore, the in-vitro immunosuppressive effect of glass-adherent mononuclear cells also could not be ruled out¹⁸ (Fig. 1), though precautions were taken to minimise the effect of suppressor T cells. In a pilot study it was found that serum from melanoma patients showing a poor response to PHA could also inhibit the lymphoproliferative response in normal individuals. This phenomenon is being investigated in detail. Since it has been suggested that the presence of free antigens or antigen-antibody complexes in patients serum may modify the antigen-specific lymphoproliferative response in tissue culture, attempts were made to detect the presence of such complexes in the serum of the patients in whom lymphoproliferative responses were studied, as shown in Table 4.

The level of circulating immune-complex was within the normal range except in 1 patient in whom the tumour was markedly necrotic. Although raised levels of immune-complexes have been reported in retinoblastoma,¹⁹ which are invariably necrotic, Dernouchamps and associates²⁰ using a different technique found that only 2 of their 7 cases of malignant melanoma of the choroid had any detectable amount of C1q binding aggregates in the blood. It would appear, therefore, that in malignant melanoma of the choroid at least an immune-complex-induced tumour enhancement may not be an important feature of its natural history. The reason we used autologous serum instead of fetal calf serum throughout this study was that the latter is known to produce a toxic effect after heat inactivation and may contain a substance which will produce nonspecific stimulation of the lymphocytes. Either effect could obscure any difference in the radioactive uptake counts between the control and the experimental tubes.²¹ Serum from healthy volunteers can be used as a substitute for autologous serum in order to exclude the presence of inhibitors, but this again is not free from problems, because the serum has to be fresh,²¹ and, furthermore, antibodies

in the allogeneic serum may react with blood group antigens on the surface of the patients lymphocytes and modify their response to tumour antigens. This limitation would be reduced, however, if the patients studied belonged to blood group O and therefore lacked group A or B antigens on the cell surface.²² Recent studies suggest, however, that immunosuppressive substance present in cancer-bearing animals have a high affinity for lymphocytes, and therefore substitution of autologous serum is unlikely to alter the lymphoproliferative response.²³ It is of interest in this context that the antigen-specific lymphoproliferative response in cutaneous melanomas is similarly of low key possibly because of weak immunogenicity of melanoma antigens.^{24,25}

An indirect macrophage migration inhibition test was carried out in only 5 cases of malignant melanoma of the uvea. The test was positive in 2 cases in which the lymphocyte transformation index was also high.

The migration inhibition test appeared to correlate with an in-vitro lymphoblastic response except in 1 patient in whom there was no evidence of lymphokine production in spite of a positive lymphocyte transformation test. Our findings do not compare with those of Manor and co-workers,¹⁷ who were able to demonstrate a macrophage migration inhibition in 7 of their 8 cases of choroidal melanoma. This may be due to the fact that they used a direct (i.e., 1-stage) migration inhibition test, which is more likely to be affected by nonspecific factors.

The lymphocytes obtained from healthy donors as well as patients with metastatic carcinoma, benign intraocular naevus, and non-neoplastic eye diseases did not show any appreciable reactivity to pooled allogeneic melanoma extract, which further supports the conclusion that the in-vitro nuclear activity seen in melanoma patients was tumour-specific and not due to stimulation by transplantation antigens.

The enhanced in-vitro activity of lymphocytes in melanoma patients correlates well with the extent of the disease, being markedly increased in every case which showed evidence of extraocular extension compared with only 5 of the 14 patients in whom the tumour was localised to the uvea. It is known that the intraocular tissues are not provided with lymphatic channels, so that the afferent limb of the immune response may be prolonged with respect to antigens originating within the eyeball. This may be partly responsible for the immunological privilege enjoyed by the eye and cause delayed sensitisation to intraocular malignancy, in which case the privilege is a disadvantage to the individual. The generally low transformation index in our patients

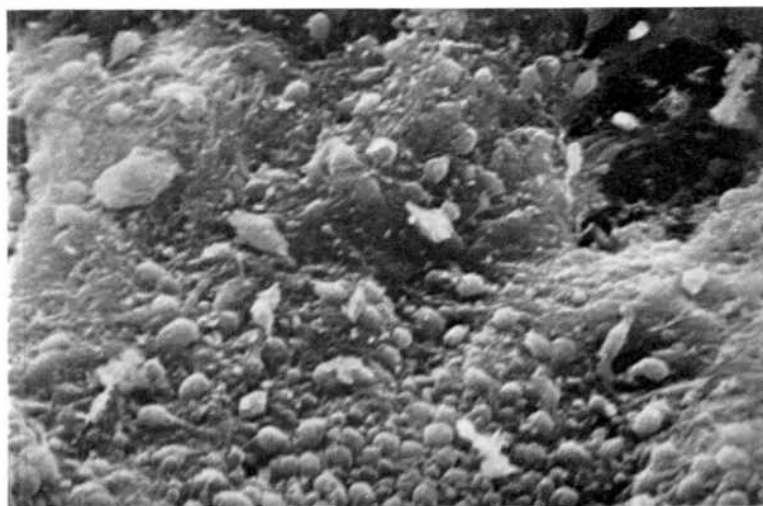


Fig. 4 Scanning electron micrograph of a malignant melanoma of the iris ($\times 516$). The arrangement of tumour cells is such that during contraction of the iris some of them may detach into the anterior chamber, where they may either become engulfed by the trabecular endothelium or enter the Schlemm's canal to reach general circulation.

should therefore be seen in the light of this background and not compared with tumours arising in other parts of the body, where a low transformation index is usually associated with generalised metastases.^{56,57}

The cell-mediated immune response in uveal melanoma appears also to be dependent on the size of the tumour and hence on the amount of antigens available. The lymphocyte transformation test was positive only in those cases in which the largest tumour diameter in contact with the sclera was 12 mm or more, while in all the negative cases the tumour was 10 mm or less in diameter apart from 2 cases where it was 11 mm and 15 mm respectively. It may also be of significance that in patients with a negative lymphocyte transformation test the tumour consisted of compact spindle cells, while in all the cases with a positive lymphocyte transformation test the tumour consisted of a varying mixture of spindle and epithelioid cells. Since epithelioid cells appear less cohesive, they may more easily become detached and lead not only to early metastasis^{58,59} but also to stimulation of the immune system. It is possible that this explanation is not applicable to melanomas of the iris, where tumour cells of both spindle and epithelioid variety or their antigenic components may be released into the anterior chamber during normal contraction and relaxation of the iris (Fig. 4) and pass into the canal of Schlemm either directly or after being taken up by the resident population of phagocytic cells in the trabecular meshwork, which include both histiocytes as well as endothelial cells.⁶⁰

The growth and metastatic property of a malignant tumour is greatly affected by the immuno-

genicity of the tumour and the immunological status of the host.⁶¹ Furthermore, it is known that antigens become more immunogenic after being processed by macrophages.⁶² It is conceivable therefore, that antigenic substances released from a tumour of the iris would have the advantage of having a head-start. This may be the reason why 2 of the 3 cases of malignant melanoma of the iris had possible evidence of sensitisation to tumour-associated antigens as compared to malignant melanoma of the choroid, in which only 45% of the patients were sensitised. Whether or not this possible early sensitisation is responsible, at least in part, for the slow growth and better prognosis in melanomas arising from the iris remains to be proved.

It is possible that infiltration of the tumour by lymphocytes and plasma cells represents an immune response aimed at eradication of a malignant lesion, such infiltration having been claimed to improve the prognosis in a variety of tumours, including those arising in the breast.⁶³ More recently Tritsch⁶⁴ produced evidence that an intense inflammatory reaction at the periphery of cutaneous melanomas reflects a favourable prognosis.

It is significant that all 10 cases giving a positive lymphocyte transformation test showed varying degrees of lymphocytic infiltration in and around the tumour, though it is not known whether the infiltration simply reflected a state of hypersensitivity or represented a favourable prognostic sign. These patients will have to be followed up for several years before any conclusion can be drawn. Histochemical and ultrastructural changes in the infiltrating lymphocytes are indicative of an in-vivo immune reaction, and fewer morphological changes

have been reported in cutaneous melanomas.⁶⁵⁻⁶⁶ We are studying the nature of the lymphocytes because it would be interesting to know whether these cells are cytotoxic lymphocytes engaged in tumour homeostasis or suppressor T cells that are involved in tumour enhancement.⁶⁷⁻⁶⁹

Contrary to an earlier belief, malignant tumours are not truly autonomous, that is, capable of growing relentlessly. Homeostasis in cancer is now a well recognised entity, and a spontaneous regression of certain tumours such as choroidal melanoma is only one aspect of this important phenomenon. It would appear that a tumour is a heterogeneous and uneven collection of cells, some of which are proliferating (i.e., taking part in the mitotic cycle) and some of which are not, and which is subject to depletion by migration and cell death.⁷⁰ Necrosis is thus not uncommon in choroidal melanoma, and does not always appear to be attributable to ischaemia.¹⁴⁻²¹ Theories have been advanced that necrosis and inflammation in choroidal melanoma are indicative of the host's attempt to destroy the tumour. It is of relevance that variable degrees of apoptosis (shrinkage necrosis) and coagulative necrosis were observed in 6 of the 21 cases of uveal melanoma, and, since the lymphocyte transformation test was positive in all of these cases, it is tempting to conclude that the necrosis was immunologically induced. Alternatively, a positive immune response is more likely when a melanoma becomes necrotic and releases large amounts of tumour-associated antigens. Since it is known that tumour cells which infiltrate and produce metastases are different from the primary tumour mass not only in their histological characteristics and karyotypic profiles but also in their susceptibility to cytotoxic drugs due to surface membrane changes and acquisition of stronger electronegative charge,⁷² it is tempting to postulate that in those cases of uveal melanoma in which there was a marked lymphoproliferative response the primary tumour contained a small pre-existing population of cells which was either more antigenic or was capable of extending outside the intraocular environment to mount an immune response.

While this may be true, there is no doubt that infiltration and metastases (in malignant melanoma) are the net results of a variety of cellular characteristics including antigenicity, susceptibility to immune-mediated lysis, anchorage-independent growth, multichromosomal abnormality, and the rate of growth.⁷²

The degree of pigmentation and the extent of mitotic activity and their correlation with prognosis have been well documented,⁵⁹⁻⁷³⁻⁷⁴ but in our study we did not find any significant correlation between

the degree of pigmentation and mitotic activity with the intensity of the lymphoproliferative response. It appears that a positive lymphoproliferative response to melanoma antigens is obtainable in about half of the patients (i.e., 12 out of 25) with malignant melanoma of the uvea. However, the lymphoproliferative response evoked by melanoma tissue was much weaker than the response seen in cultures stimulated by PHA and PPD. This may mean that melanoma antigens are poorly immunogenic. The differences between positive and negative responses may be markedly reduced if the antigen is not prepared correctly and the proper culture techniques are not followed meticulously. The best results are obtained when the lymphocyte culture is challenged 24 hours after incubation, since by this time most of the suppressor T cells are ineffective. A good lymphoproliferative response was obtained only when lymphocytes, maintained in a gaseous phase consisting of 5% carbon dioxide in air, were harvested 6 days after the addition of the antigen. Since the test was negative in about half of the histologically confirmed cases of uveal melanoma, a negative immunological result does not exclude the diagnosis of malignancy. Nevertheless, the fact that we did not obtain any false positive results is encouraging, though the control series consisted of only 12 cases; further work is required before a conclusion is warranted.

It seems that the patients do not mount a reasonable degree of cell-mediated immunological response to melanoma antigens unless the tumour has extended outside the eyeball and become accessible to immunologically competent cells. It is not surprising, therefore, that, although the response of the lymphocytes in these patients was tumour-specific, it was largely ineffective in controlling tumour growth.

This peculiar response of uveal malignancy when compared with malignant tumours elsewhere in the body can be explained at least in part by postulating that both the afferent and efferent limbs of the immune response in the eye may be subject to delay and modification because of the absence of lymphatic channels in intraocular tissues.

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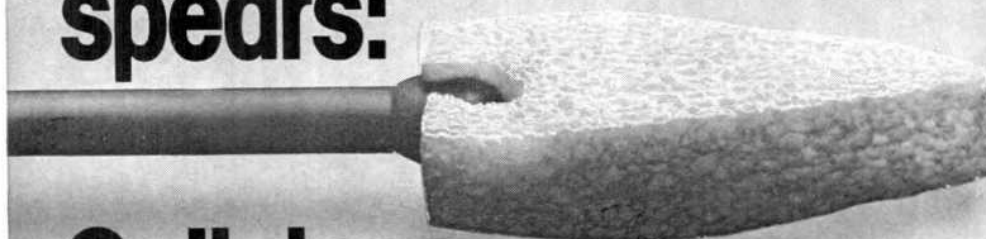
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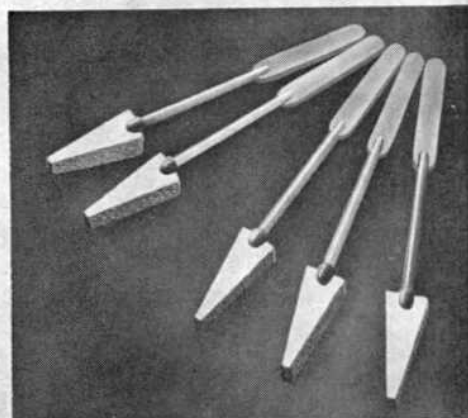


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2 Intra-ocular pressure is maintained at satisfactory levels many patients can then be placed on once-a-day therapy. Because of naturally occurring diurnal variations in intra-ocular pressure, satisfactory response is best determined by measuring the intra-ocular pressure at different times during the day.

3 Clinical trials have shown the addition of TIMOPTOL to be useful in patients who respond inadequately to maximum antiglaucoma drug therapy.

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Use of the Arden grating test for screening

ROBERT G. WEATHERHEAD

From Moorfields Eye Hospital, City Road, London EC1V 2PD

SUMMARY One hundred and forty patients were referred for a clinical evaluation of their eyes, having produced high scores on screening by the Arden grating test (AGT). In these patients 66% of the eyes were found to be normal, 31% abnormal, and 3% indeterminate on clinical examination. Suitable criteria for referral for clinical examination were determined and the recommended scores are: (a) A total AGT score of >80 ; (b) One or more plates scoring >17 ; (c) A difference between the two eyes of >13 . With these criteria at least 95% of the abnormal eyes will be detected. As a screening test the AGT is equal to the Snellen distance visual acuity test at separating the normal group from the abnormal group, and on the recommended criteria the AGT gives a better ratio of false positives to false negatives.

The Arden grating test is a subjective clinical test of visual function introduced in a portable book form by Arden and Jacobsen in 1976.^{1,2} The principle of the test is the measurement of contrast sensitivity by sine-wave gratings (Fig. 1). In this study a standard set of 6 plates in book form were used under controlled illumination conditions. The visual threshold for the gratings was measured for each of the 6 different spatial frequencies. Each eye was tested separately. The test yields a score, and there are many factors which affect this score. Among these are the age of the patient,³⁻⁶ number and form of the plates,^{3,4} illumination conditions, and the disease process from which the patient is suffering.^{1,3-5,7,8} The value of the AGT as a screening test for use by general practitioners and others is under consideration, and this aspect, as well as the identification of guidelines for clinical use, were the aims of this study.

Materials and methods

A total of 140 patients from the London area underwent a careful ophthalmic assessment at Moorfields Eye Hospital after a screening procedure done either in a general practitioner's rooms or in a general eye clinic. Seventeen general practitioners referred patients.

SCREENING

From an unrecorded number of patients visiting their general practitioners 138 patients were found to score above the screening criteria on the AGT. Of these, 73 (52.9%) were screened because they presented with an eye complaint, 48 (34.8%)

because they were considered high risk—for example, had hypertension or angina—and 17 (12.3%) were found on random screening.

The criteria for referral were arbitrarily taken at

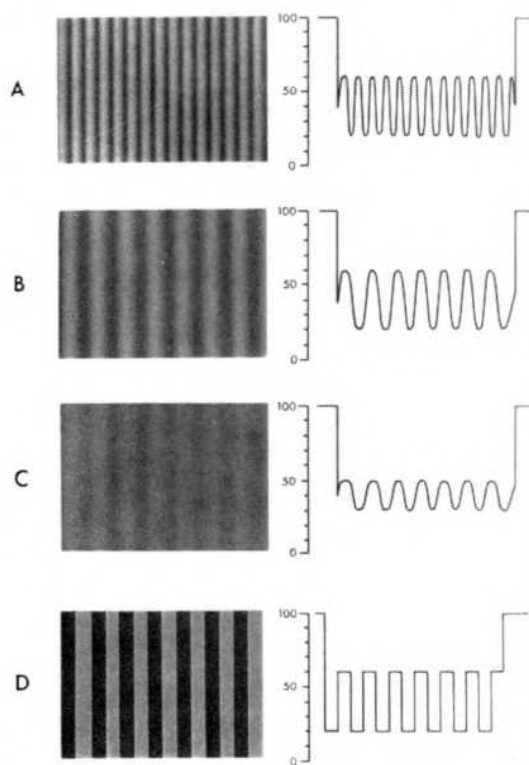


Fig. 1 Diagram showing the difference between sine-wave and square-wave gratings.

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(i) score over 78 in any one eye (it should be noted that the normal value previously claimed was 82 and that the value of 78 was set to include some false positives); (ii) asymmetry of scores in the 2 eyes greater than 10; (iii) a score on any plate over 16. An example of the scoring system used for the AGT is given in Table 1, where 20 was the value given for any plate on which the gratings were not visible. In some studies this value is taken as 25, so that their maximum score possible is 140.

A further 2 patients from a general eye clinic were seen, thus giving a total of 140 patients.

EXAMINATION

At Moorfields Eye Hospital the patients had a repeat AGT done under standard conditions,

Table 1 *Example of scoring system*

Plate	Right eye	Left eye
2	11	12
3	8	10
4	12	18
5	10	14
6	12	17
7	12	Not seen
Total	65	91

Table 2 *The results of clinical examination*

Results					
Number of eyes tested	280				
Abnormality found	86 (31%)				
Indeterminate	10 (3%)				
Normal	184 (66%)				
Reason for abnormality	Snellen VA				
	6/5	6/6	6/9	>6/9	
Cataract	46	2	6	16	22
Macula	10	0	2	3	5
Optic nerve disease	7	1	—	2	4
Field defect	7	2	3	2	—
Retinal	5	—	2	2	1
Corneal	3	—	—	3	—
Glaucoma	3	—	—	1	2
Optical	2	—	—	1	1
Amblyopia	2	—	—	—	2
Embolic	1	—	1	—	—
Reason for being indeterminate					
Suspected amblyopia				3	
Previous ECT and leucotomy				2	
Colour blindness				2	
Personality problem with unreliable AGT scores				1	

Table 3 *The age distribution of the patients tested*

Age group	Total	N	A	I
15-19	2	1	1	—
20-24	8	7	—	1
25-29	10	9	1	—
30-34	6	6	—	—
35-39	14	12	2	—
40-44	16	11	3	2
45-49	10	10	—	—
50-54	26	24	2	—
55-59	26	19	6	1
60-64	38	20	14	4
65-69	62	38	23	1
70-74	36	18	17	1
75-79	14	7	7	—
80-84	12	2	10	—
Total	280	184	86	10

N = Normal. A = Abnormality found. I = Indeterminate.

followed by a thorough ophthalmological examination. Those patients requiring further investigative tests or treatment were referred to the various departments available at Moorfields Eye Hospital—for example, the electrodiagnostic department, the retinodiagnostic department.

FOLLOW-UP

On the basis of this clinical examination the patient was considered normal, abnormal, or indeterminate. Those patients who had a normal examination but a high AGT score were recalled 2 to 12 months later (average 6 months), and a repeat AGT and visual assessment was done.

There were 71 patients in this group. Fifty-two patients reattended and were found to have different AGT scores, though clinically they were unchanged. Nineteen patients failed 3 times to reattend for follow-up.

Results

Seventy-one patients who were clinically normal but who had high AGT scores were recalled (Table 2). Nineteen failed to reattend, 1 had died, and 1 had had a stroke. Fifty-two reattended (104 eyes). Eighty-one were better (by 1-21, average 10), 17 were worse (by 1-28, average 8), and 6 had the same score.

Table 3 shows the age distribution of the patients tested and the distribution of the normal and abnormal groups (most are in the elderly age group).

Table 4 shows the distribution of the AGT scores and the breakdown of the group into normal and abnormal groups. Considering each of the groups

from this population the following emerges. (a) Normal eyes ($n=184$): mean 76.8, median 75, standard deviation 8.7. (b) Abnormal eyes ($n=86$): mean 95.5, median 95, standard deviation 8.3. (c) Indeterminate eyes ($n=10$).

The distribution of Snellen distance visual acuity scores is given in Table 5.

Fig. 2 and Table 6 show that there is a highly significant difference in the separation of the normal and abnormal groups by the Arden grating and Snellen distance visual acuity tests.

A cumulative frequency graph and a table were constructed from the data to show the false positive and false negative rates for the AGT and the Snellen test (Fig. 3 and Table 7). A false positive

Table 5 The distribution of the Snellen distance VA scores

Snellen distance visual acuity	N	A
6/5	81	5
6/6	65	14
6/9	33	30
6/12	5	13
6/18	—	14
6/24	—	4
6/36	—	2
6/60	—	1
<6/60	—	3
Total	184	86

N = Normal, A = Abnormality found.

Table 4 The distribution of the AGT scores

AGT score	Total	N	A	I
56-60	2	2	—	—
61-65	9	9	—	—
66-70	30	28	1	1
71-75	60	57	3	—
76-80	54	46	6	2
81-85	26	13	10	3
86-90	28	15	11	2
91-95	19	5	13	1
96-100	15	6	8	1
101-105	17	1	16	—
106-110	11	2	9	—
111-115	5	—	5	—
116-120	4	—	4	—
Total	280	184	86	10

N = Normal, A = Abnormality found, I = Indeterminate.

Table 6 Comparison of the AGT and Snellen scores

	AGT		Snellen	
	Normals	Abnormals	Normals	Abnormals
Number	184	86	184	86
Mean	76.8	95.5	30.44*	18.38*
Standard deviation	8.7	8.3	6.30	8.79
Standard error of the mean	0.64	0.89	0.46	0.95
Difference between means	18.7		12.06	
<i>Difference between means</i>				
Combined standard error of the means				
= <i>t</i> value	16.69		12.85	
Associated P value	P<0.001		P<0.001	

*In cycles/degree assuming 6/6 = 30 cycles/degree.

This analysis means that there is a highly significant difference in the separation of the normal and abnormal groups by the 2 tests.

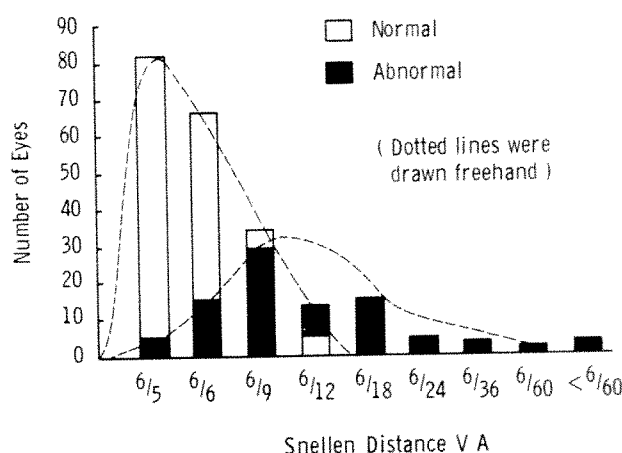
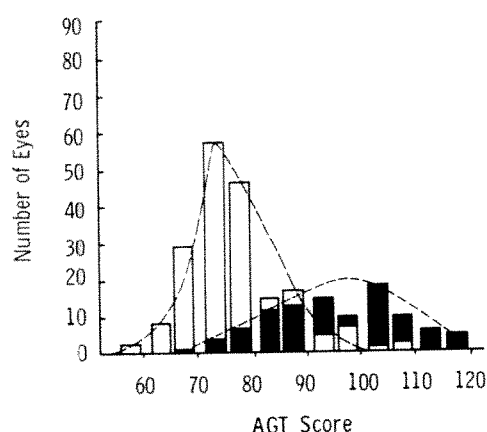


Fig. 2 A comparison of histograms constructed from the AGT scores and Snellen test scores achieved by the same patients.

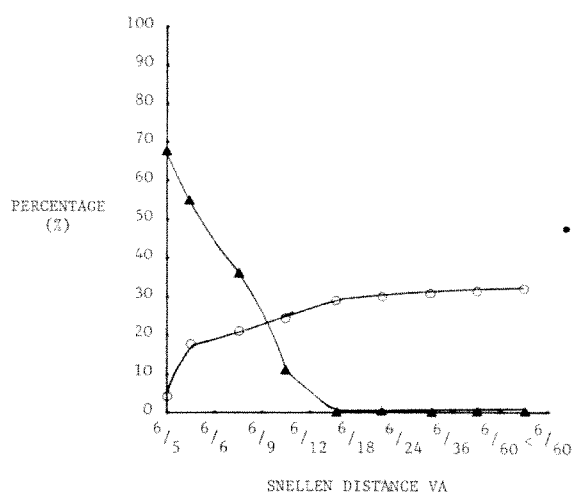
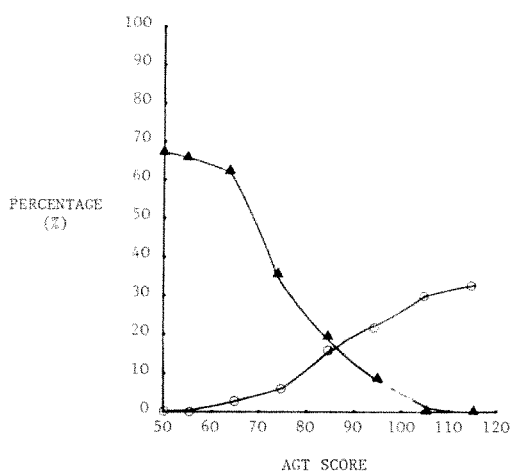


Fig. 3 Cumulative frequency graph showing the curves for the false positive and false negative rates. $\blacktriangle$ = False positive rate. $\triangle$ = False negative rate. Connecting lines were drawn freehand.

Table 7 False positive and false negative rates for the AGT and the Snellen test

		False positive	False negative
AGT	below 50	184/270 = 68.1%	0%
	≤ 60	182/268 = 67.9%	0/11 = 0%
	≤ 70	145/230 = 63.0%	1/40 = 2.5%
	≤ 80	42/118 = 35.6%	10/152 = 6.6%
	≤ 90	14/69 = 20.3%	31/201 = 15.4%
	≤ 100	3/37 = 8.1%	52/233 = 22.3%
	≤ 110	0%	77/261 = 29.5%
	≤ 120	0%	86/270 = 31.8%
Snellen test	6/5	184/270 = 68.1%	5/86 = 5.8%
	6/6	103/184 = 55.9%	19/105 = 18.1%
	6/9	38/105 = 36.2%	49/228 = 21.5%
	6/12	5/42 = 11.9%	62/246 = 25.2%
	6/18	0%	76/260 = 29.2%
	6/24	0%	80/264 = 30.3%
	6/36	0%	82/266 = 30.8%
	6/60	0%	83/267 = 31.1%
	$< 6/60$	0%	86/270 = 31.8%

is a person who is clinically normal yet scores above the criteria on the test, and a false negative is one who is clinically abnormal and scores below the criteria on the test.

Fig. 4 and Table 8 show the effect of using 1 or more plates scoring 17 or more. It can be seen that the 2 curves separate further with the increase in number of high scoring plates.

Using the difference in scores between the two eyes we see among the 20 patients who had one eye normal and the fellow eye abnormal clinically the

range of scores was -8 to +32, mean +15.1; while among the 80 patients with both eyes normal on clinical examination the range of scores was 0 to

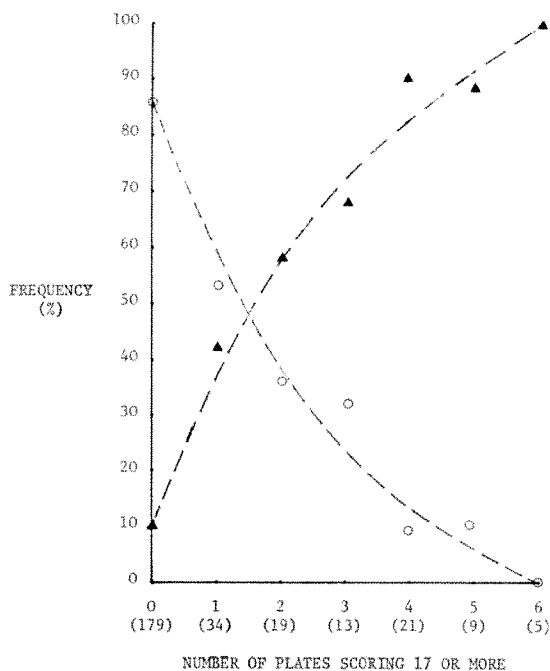


Fig. 4 Graph showing the differentiating effect of using the individual plate scores. There are insufficient numbers in some groups, but the trend can be seen. $\blacktriangle$ = Abnormal eyes. $\circ$ = Patients with normal eyes. Connecting lines were drawn freehand.

+16, mean +3.3. These two groups are compared in Fig. 5 and Table 9.

There are 'grey areas' where the AGT score cannot necessarily be correlated with a detected abnormality for example, in migraine with a transient field defect but no residual damage. In this study 1 patient with a very high AGT score had 6/5 vision in both eyes and normal Goldmann and Friedmann fields. Another example is the presence of fine macular drusen, again with 6/5 vision. The AGT may be detecting an abnormality before that abnormality is affecting other visual function parameters. There were other disease processes which may have affected the AGT score but which could not be

Table 8 *The effect of using supplementary screening criteria: using the number of plates scoring 17 or more*

Number of plates scoring 17 or more	Total number in group	N	A	I
0	179	152	20	7
1	34	18	14	2
2	19	7	11	1
3	13	4	9	—
4	21	2	19	—
5	9	1	8	—
6	5	—	5	—
Total	280	184	86	10

N=Normal. A=Abnormality found. I=Indeterminate.

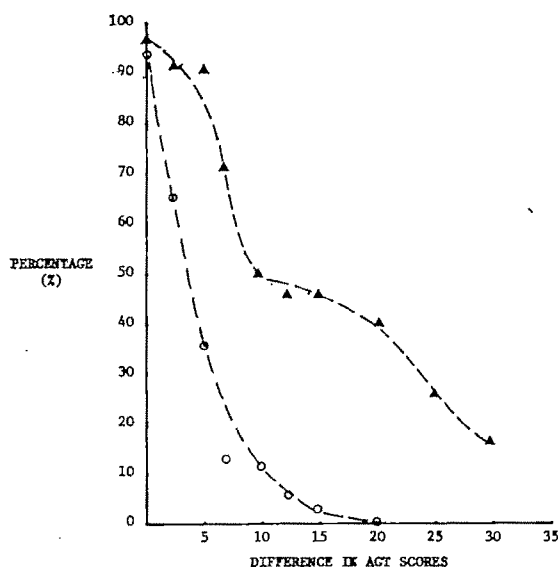


Fig. 5 Cumulative frequency graph plotting the differences between the 2 eyes. ▲ = Patients with one eye normal and fellow eye abnormal. ○ = Patients with both eyes normal. Connecting lines were drawn freehand.

Table 9 *The effect of using supplementary screening criteria: using the difference between the 2 eyes*

Difference	Both eyes normal	One eye normal/ other eye abnormal
0-2.5	75/80 = 93.75 %	19/20 = 95 %
2.5-4.9	52/80 = 65 %	18/20 = 90 %
5-7.5	29/80 = 36.25 %	18/20 = 90 %
7.5-9.9	13/80 = 16.25 %	14/20 = 70 %
10-12.5	9/80 = 11.25 %	10/20 = 50 %
12.5-14.9	4/80 = 5 %	9/20 = 45 %
15-19.9	2/80 = 2.5 %	9/20 = 45 %
20-24.9	0 %	8/20 = 40 %
25-29.9	0 %	5/20 = 25 %
30+	0 %	3/20 = 15 %

confirmed—for example, a diagnosis of suspected vertebrobasilar insufficiency. This is essentially a clinical diagnosis, and proving this would entail angiography with all its inherent risks.

Discussion

When using the total AGT score, to determine the best value to use it is necessary to consider: (i) a clinically acceptable level of false negatives; (ii) the importance of those false negatives; (iii) the ratio of false positives to false negatives.

(i) Few guidelines are available in setting an acceptable false negative rate for visual screening, but if the level were set at 5% then the corresponding value for the AGT is 79. The equivalent on the Snellen test is 6/5.

(ii) Table 10 was drawn up to examine those abnormalities missed, to see whether this is critical or not. Three of the patients had conditions which require early investigation, namely, optic atrophy, optic nerve head infarct, and central retinal vein occlusion, and in this regard the value of 79 is too high. However, a lower value would mean the need to examine more people.

(iii) At 79 the ratio of false positives to false negatives is approximately 8:1 for the AGT, and the corresponding ratio for the Snellen is approximately 13:1.

When using the supplementary criteria to aid the detection of abnormal eyes:

(i) Number of plates scoring ≥ 17 . The results reflect the overall trend in the total AGT score, that is, the greater the number of high-scoring plates the greater the AGT value and the more likelihood there is of an abnormality. However, 3 out of the 9 false negatives on the AGT score alone would have been detected by this added criterion (Table 10).

(ii) Difference between the 2 eyes. 95% of the

Table 10 Analysis of those abnormals who scored less than 79 on the AGT

AGT score	Disease	Difference between the 2 eyes	Number of plates ≥ 17	Snellen
79	Cataract +	4	1	6/18
79	Cataract +	2	1	6/9
79	Optic atrophy +	19	0	6/5
78	Probable old infarct of optic nerve head	10	0	6/9
76	Cataract +	5	0	6/5
75	Cataract +	6	1	6/18
75	Compensated CRVO	2	0	6/6
73	Anterior corneal dystrophy ++	4	0	6/9
69	Anterior corneal dystrophy ++	4	0	6/9

CRVO = Central retinal vein occlusion.

normal group have a difference of <13 between their two eyes. A further one false negative was detected by this extra criterion. It is interesting to note that a further three false negatives had a Snellen visual acuity of worse than 6/6.

In summary then, the criteria which are recommended for use in screening are: (1) Total score of ≥ 80 ; (2) one or more plates scoring ≥ 17 ; (3) a difference between the 2 eyes of ≥ 13 .

PLACE OF THE AGT IN A CLINICAL SETTING
The AGT is of value as a screening test because the ratio of false positives to false negatives is better than with the Snellen, though both tests are good at separating normals from abnormals.

It should be noted here that in order to make the comparison of AGT and Snellen tests as stringent as possible the patients were considerably encouraged to achieve their best Snellen and AGT acuities, and this involved refraction in many cases (though

the AGT result does not greatly depend on refraction. Since most screeners will have neither the time nor the facilities to do this, there is likely to be a difference between their results and those recorded here. With the score obtained by the general practitioner the average difference was 10.3 AGT units in this study (27% of the general practitioner scores were lower, 69% higher, and 4% the same). This means that in testing by a general practitioner the AGT would yield more false positives, and this would tend to counteract any slight difference between the AGT and the Snellen test for screening purposes. Hence there is little to be gained from its use here. However, it would seem logical to use the AGT as a supplementary test in general and special eye clinics, such as retinal, macular, glaucoma, and neuro-ophthalmology clinics.

I should like to thank Mrs Sandra Max, Mrs Elizabeth Cosgrove, Dr Conrad Harris, Professor G. Arden, the secretaries, and the staff of Moorfields Eye Hospital for their help in this project.

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Clinical trial of the use of rotating grating patterns in the treatment of amblyopia

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SUMMARY Recent reports suggest that the vision in amblyopia can be significantly improved by brief weekly periods of occlusion of the good eye while the child performs concentrated visuomotor tasks against a background of rotating gratings. We have conducted a controlled trial to investigate the role played by the gratings in this procedure. One group (n=33) of amblyopic children viewed a series of rotating gratings during treatment, while the other group (n=27) performed exactly the same visuomotor tasks against a homogeneous grey background. Particular attention was placed on the choice of tests of visual acuity in order to highlight the crowding phenomenon that is a characteristic feature of the visual loss in amblyopia. The chart selected for this purpose was the Bailey-Lovie chart in which the number of letters on each line was held constant and the letter sizes and spacing were graded in equal logarithmic steps. Some improvement in vision occurred in almost all patients in either treatment group, a finding that provides support for recent claims for the effectiveness of minimal occlusion therapy. The difference between the improvement in vision of the 2 groups, averaged across all tests, was not statistically different. On only 1 of 6 acuity scores was a statistically significant difference observed in favour of the grating treatment group. However, this was observed only on patients with better than 6/60 vision where the overall improvement was itself very small. There was no detectable difference between the 2 groups either in the rate of improvement of vision or in the tendency of the vision to be maintained or even improved after cessation of treatment. Since the patients treated with gratings improved little or no more than those in the control group, we conclude that most of the visual recovery was promoted by some other aspect(s) of the procedure.

The last few years has seen a revival of interest in the use of brief or minimal periods of occlusion for the treatment of amblyopia.¹⁻³ A particularly promising variant on this procedure which resulted in a dramatic improvement in the visual acuity of the amblyopic eye was reported by Banks *et al.*⁴ The technique required occlusion of the nonamblyopic eye once a week for only 7 minutes, during which time the child viewed a series of rotating square-wave gratings of different periods or sizes that were located immediately behind a clear plastic plate on which the child drew or played games in order to maintain fixation on the gratings. Although this procedure involved only a slight alteration to the existing practice at Addenbrooke's Hospital, Cambridge, of having the child perform concentrated

visuomotor tasks for periods of 20 minutes while the good eye was occluded, the rationale for the treatment was very different. On the basis of current knowledge of the neural mechanisms by which the visual world is encoded by the normal visual system it was thought that the grating patterns, as they rotated, would act as potent stimuli for spatial frequency and orientationally selective cells in the visual cortex. It was conjectured that the improvement that occurred in the vision of the amblyopic eye with this treatment was due to the intense and sequential stimulation by the rotating grating patterns of the visual cortical cells maintaining functional connection with the amblyopic eye.^{5,6}

In further publications the authors^{6,7} reported that 73% of a sample of amblyopic patients achieved an acuity in their amblyopic eye of 6/12 or better both for distance and near vision after only 3 treatments of 7 minutes' duration. The number of

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treatment sessions required to achieve the maximum improvement in acuity was very low, the average being 5, with a range of from 1 to 40.⁷ This contrasted with the much longer time course of the improvement (average 13 weeks) achieved with minimal occlusion therapy. Furthermore, it was reported that the visual acuity often tended to improve even further and not regress after the course of treatment with gratings.

Independent pilot studies conducted at the Royal Children's Hospital and at the National Vision Research Institute in Melbourne confirmed that startling improvements in vision could be produced in many cases of amblyopia by use of this procedure. Although the gratings have been stressed as the most important aspect of this procedure, other factors, acting either alone or in concert, could have contributed to the observed improvement in vision. These other possible factors include the total period of occlusion each week (treatment duration plus visual function testing duration), the intense nature of the visual tasks forced upon the amblyopic eye during the periods of occlusion, and the visually guided motor tasks engaged in by the patient during the treatment session. However, since all of these factors were operating in the earlier treatment procedures that were practised at Addenbrooke's Hospital, it seemed that the grating stimuli viewed by the patients during treatment were producing the improvement in vision. Consequently, we decided to investigate directly, in the manner described below, the role played by the rotating gratings in the new treatment procedure. At the same time we made an effort to eliminate the effects of any inadvertent bias that could be introduced by the clinicians by conducting a 'blind' trial.

Materials and methods

The study was conducted in Melbourne at the Royal Children's Hospital (RCH) and the National Vision Research Institute of Australia (NVRIA). A total of 67 children with amblyopia of various causes were randomly assigned to 1 of 2 groups of approximately equal size. Both groups received weekly treatments, one with rotating gratings and the other with a uniform grey disc; all other aspects of the treatment procedure being the same for both groups. In order to control for any inadvertent bias introduced by the clinicians the trial was conducted as a 'blind' procedure: the clinician testing each patient's visual capacities was kept unaware of the nature of the treatment applied, while the clinician that supervised the treatment was unaware of the results of the visual tests. Seven children failed to

complete more than 3 treatments and so have been excluded from further consideration. The age distribution of the 60 children (33 in the test group and 27 in the control group) who completed 6 treatment sessions is displayed in Fig. 1. The mean age (8 years) and the range (5 to 14 years) were both slightly greater than the group of patients treated in Cambridge.⁶ The distribution of distance full-line and single letter acuities prior to commencement of treatment is shown in Fig. 3. A few patients were unable to read correctly a full line of letters at any distance; in these cases an acuity score was assigned based on the part-line score (see 'Results'). In 27 of the children (45%) the amblyopia was associated with strabismus, while in 9 cases (15%) it was accompanied by anisometropia (defined as a difference of 1.5 D or more in the spherical, or 1 D in the cylindrical refraction), and in 21 cases (35%) it was accompanied by both strabismus and anisometropia. There was little difference in the initial visual acuities of the cases with strabismus and those with strabismus and anisometropia, but in those cases of anisometropia alone the visual acuity was always 6/19 or better. In 3 cases (5%) no cause could be found for the amblyopia, and in these the visual acuity was 6/12 or better. In 43 cases (72%) there was a history of previous surgical treatment for strabismus, or occlusion therapy, or both. There was no significant difference in the distribution of visual acuities between those cases that had been treated before with occlusion and those that were untreated.

At the initial consultation a full history of the visual problem was obtained, a full ocular examination was performed, the refraction was determined

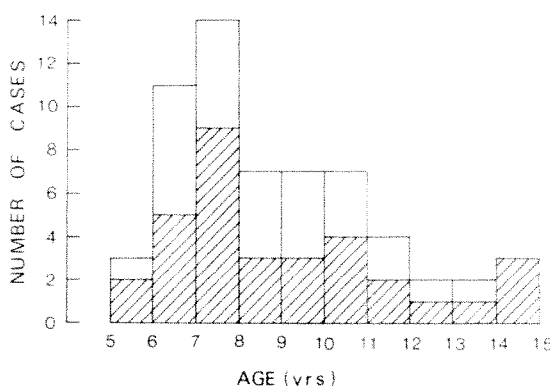


Fig. 1 Age distribution of the 60 children that completed 6 treatment sessions. Children treated with rotating gratings are depicted by hatched bars. The height of the open bars above the hatched bars depicts the number of children in each age group that viewed the grey disc during treatment.

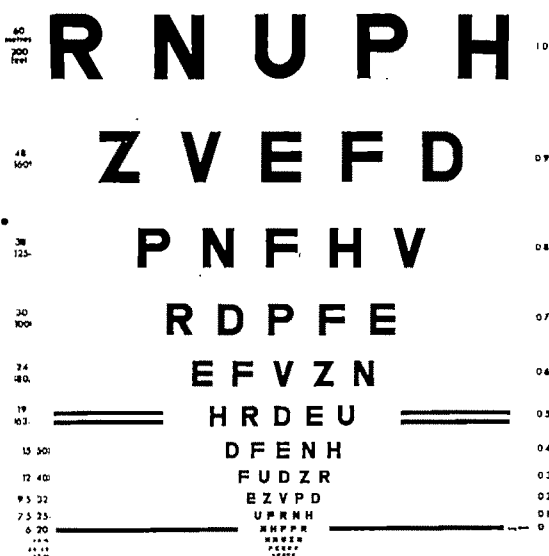


Fig. 2 An example of the Bailey-Lovie chart.¹¹ See text for description.

under cycloplegia when indicated, and a variety of visual functions were tested as described below. Considerable thought was given to the testing of visual acuity particularly in order to score visual improvement equally for all grades of visual acuity. For this reason standard Snellen test charts were not used routinely because the differences in letter size between consecutive lines do not correspond to any regular pattern (BS 4274, British Standards Institution, 1968). Furthermore, it is likely that the contour interaction effects that are characteristic of amblyopia⁸⁻¹⁰ would not be constant for each line with such charts because of the unequal number of letters on each line and the frequent lack of a constant relative spacing of letters. In fact conventional charts contain only 1 letter of the largest size (6/60) and 2 of the second largest (6/36), making it impossible to differentiate between the performance for single letters and that for a row of letters. For these reasons the chart (Fig. 2) described by Bailey and Lovie¹¹ was used for determining distance vision. This is characterised by an equal number of letters (5 in each row) and by a regular logarithmic scaling in 0.1 log unit of both the size and spacing of the letters of each line as well as the separation between lines. Consequently, there are 10 equally graded letter sizes from 6/60 to 6/6, the intervening sizes being 6/48, 6/38, 6/30, 6/24, 6/19, 6/15, 6/12, 6/9.5, and 6/7.5. This chart highlights the contour interaction effects characteristic of amblyopia, and it has the additional advantage of simplifying the scoring of acuities of less than 6/60. As the child

approaches the chart by a distance corresponding to a change of 0.1 log unit, the letter sizes alter by an equivalent amount, thus allowing easy conversion to the usual numerator of 6. For example, on viewing the chart at 4.8 metres the 6/6 letters are equivalent to 6/7.5 and the top row of letters is equivalent to 6/75; similarly at 3.8 metres, 6/95; and at 3 metres, 6/120, etc.

Characteristically amblyopes are unable to read a full line of letters below a certain level but are able to read a few smaller letters correctly, usually those at either end of a row or occasionally in the middle of a row. We therefore recorded the lowest line in which only 1 or more letters could be seen ('part' score), as well as the lowest full line of letters read ('full' score).

The acuity for single letters was measured using the Sheridan-Gardiner series of plates. These have 3 letters corresponding to each size, and are obtainable only in the conventional Snellen sizes. Separate acuities were recorded depending on whether all ('full' score) or only some ('part' score) of the letters of any one size could be read. Near visual acuity was measured at a distance of 33 cm by the Sheridan-Gardiner near test, which has 6 letters of each size corresponding to the usual Snellen test types. As with the other tests, full and part acuities were recorded.

Tests of stereopsis were made either by the Titmus plates alone (RCH) or by the Titmus, Toegepast Natuurwetenschappelijk Onderzoek (TNO), and Frisby tests (NVRJA). In addition measurements of contrast sensitivities and acuity for sine-wave gratings were made on patients examined at the National Vision Research Institute in a manner described in detail elsewhere.¹² The results of these particular measurements will be described in detail in a later publication (Howell, Mitchell, and Keith, in preparation).

For assessing visual acuities and for treatment the nonamblyopic eye was occluded with an opaque disc, patch, or plaster, except when there was latent nystagmus, when semitransparent tape was placed over the spectacle lens to blur vision to less than 6/60.

The treatment was commenced when all the necessary data had been obtained and after any significant refractive error had been corrected (1 dioptre or more). The child was seated in front of a specially built device on which the appropriate disc could be placed immediately behind a clear plastic plate. The grating discs, which were rotated at 1 revolution per minute, were 20 cm in diameter and hence slightly larger than those employed in previous investigations.^{4*} There were 6 gratings in all, the period of each differing from the next by a

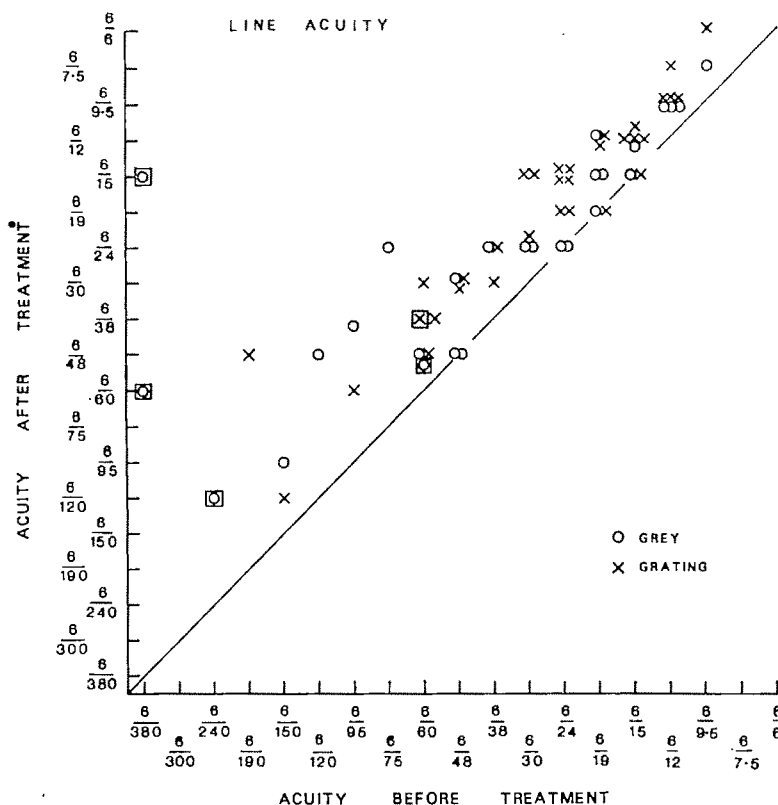


Fig. 4 Initial and final distance full-line acuity scores measured on the Bailey-Lovie chart at 6 m after 6 treatment sessions. Patients that viewed rotating gratings during treatment are depicted by cross symbols, while those that viewed a homogeneous grey disc are indicated by open circles. The line at 45° indicates no improvement. The amount of any improvement is thus given by the vertical displacement upwards from this line. Symbols outlined by squares depict subjects on whom it was possible to obtain only initial 'part' line acuity scores.

Fig. 5 The distance single letter scores before and after 6 treatment sessions. Symbols are as in Fig. 4. The amount of any improvement in vision is given by the vertical displacement upwards from the line at 45°. Symbols outlined by squares depict subjects on whom it was possible to obtain only 'part' scores.

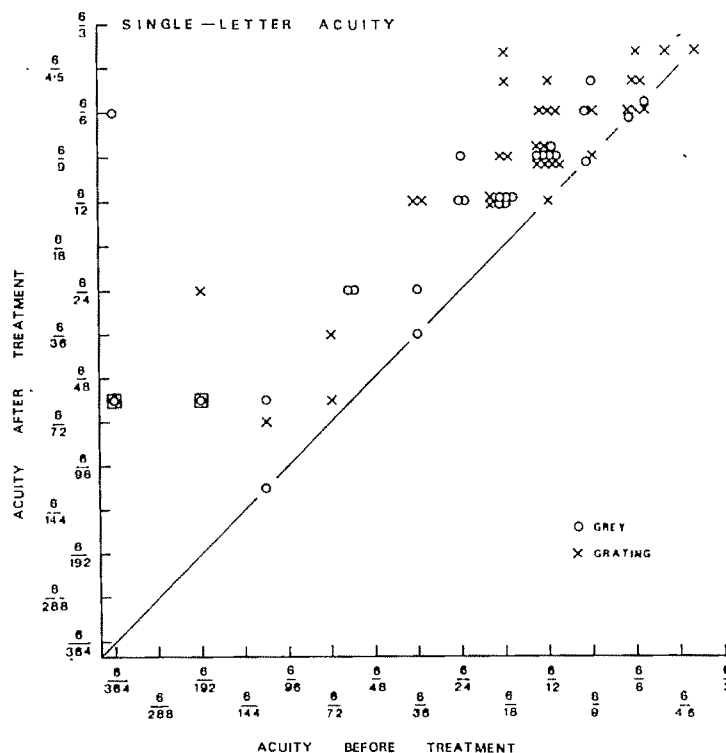
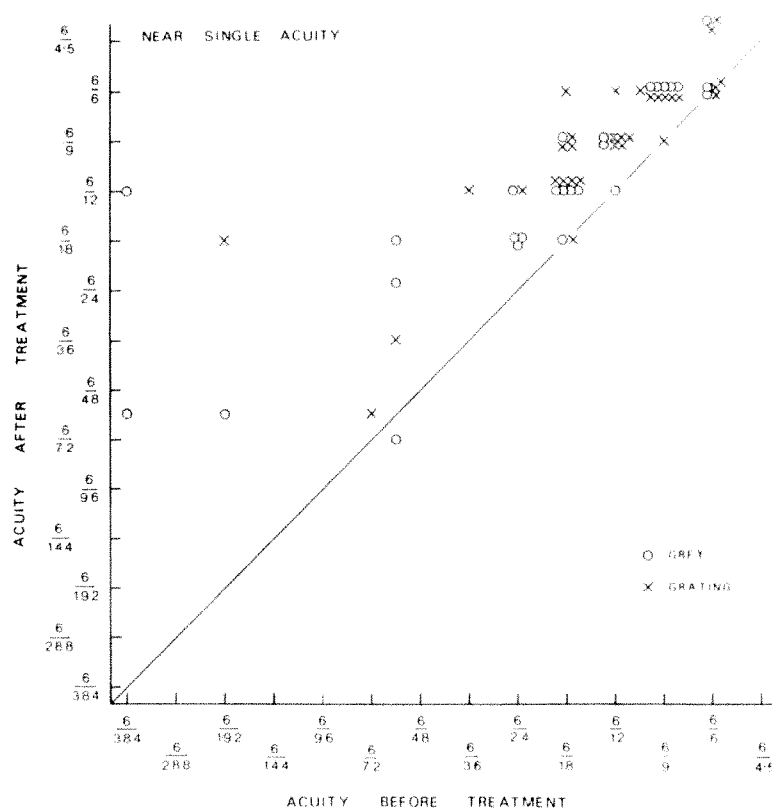


Fig. 6 Near acuity measured with the Sheridan-Gardiner near test before and after the 6 treatment sessions. Symbols are as in Fig. 4. The amount of any improvement in vision is given by the vertical displacement upwards from the diagonal line.



A quantitative comparison was made between the test group and control group and the results are shown in Table 1. For each subject the improvement in visual acuity between the initial and final assessment was expressed in terms of the ratio of the letter sizes on a logarithmic scale. This was made easy in the case of the distance line acuities since the rows of letters on the Bailey-Lovie chart are already scaled in equal logarithmic steps. An improvement of 1 line on this chart is equivalent to 0.1 log unit, while a 3-line improvement is equivalent to 0.3 log unit, or a halving of the letter size. To score the improvement in the single letter and near visual acuities, the Snellen notations were first converted to their logarithmic equivalents. Only patients on whom actual full or part acuity scores could be obtained were included in the quantitative comparison shown in Table 1. The patients were at first considered in 4 groups according to whether their initial distance full line acuities fell between the following bounds: less than 6/60, between 6/60 and 6/38, between 6/30 and 6/15, or 6/12 or better. However, since the degree of improvement observed in the latter three groups proved to be so similar, these results were combined

for the analysis which is shown in Table 1. In this table the mean improvement is given for each test of visual acuity: distance 'full' and 'part' line acuity, distance 'full' and 'part' single-letter acuity, and near single-letter 'full' and 'part' acuity. The standard deviation of the scores is shown adjacent in brackets for the subjects in the 6/60 plus group, while only the range has been shown for the 6/60 minus group since the numbers were so small.

As was apparent from Figs. 4, 5, and 6, the mean improvement in the 6/60 minus group was much more marked than among the subjects with better than 6/60 vision. The average improvement for the former group was 0.48 log unit (equivalent to 4.8 lines on the Bailey-Lovie chart) for patients treated with either rotating gratings or the grey disc, while in the 6/60 plus group the average improvement was only 0.17 log unit (1.7 lines) for subjects treated with gratings and 0.14 log unit (1.4 lines) for those receiving treatment with the grey disc. Within the group with vision of 6/60 or better there was no obvious difference in the degree of improvement between those patients treated with gratings or the grey disc except on the distance full-line acuity measures. On this particular test the 29 patients

Table 1 Mean improvement in acuity scores for each visual acuity test (log units)

Treatment group	Acuity test						All tests
	DLF	DLP	DSF	DSP	NSF	NSP	
6/60 Minus group (range of scores in brackets)							
Gratings	0.33 (0.1-0.7)	0.3 (0.1-0.8)	0.38 (0.1-0.9)	0.5 (0.2-1.0)	0.4 (0.1-1.0)	0.57 (0.2-1.2)	0.41
Number of cases (4)	3	4	4	4	4	3	
Grey	0.38 (0.2-0.5)	0.53 (0.1-1.4)	0.48 (0.1-1.8)	0.48 (0.3-0.8)	0.49 (0.1-1.5)	0.53 (0.1-1.6)	0.48
Number of cases (8)	4	8	6	6	7	6	
6/60 Plus group (standard deviation of scores in brackets)							
Gratings	0.15 (0.084)*	0.13 (0.1)	0.2 (0.19)†	0.2 (0.14)	0.18 (0.13)	0.16 (0.14)	0.17
Number of cases (29)	29	29	29	22	29	22	
Grey	0.08 (0.09)*	0.11 (0.06)	0.16 (0.13)†	0.18 (0.16)	0.16 (0.09)	0.14 (0.15)	0.14
Number of cases (19)	19	19	19	18	19	16	

The acuity tests above were: distance line full (DLF), distance line part (DLP), distance single letters full (DSF), distance single letters part (DSP), near single letters full (NSF), and near single letters part (NSP).

*For 6/60 plus group, DLF $t=2.86$, $0.01 < P < 0.001$. †For 6/60 plus group, DSF $t=0.8$, $0.5 < P < 0.1$.

treated with gratings improved an average of 0.15 log unit, while those treated with the grey disc changed somewhat less (0.08 log unit). The small difference between the average improvement of the 2 treatment groups on this one particular test was, however, statistically significant at the 0.005 level on both a Student t test and the nonparametric Mann-Whitney U test.

Further analysis of the data from the group of patients with better than 6/60 vision revealed no obvious difference in the degree of improvement among children that had received previous occlusion therapy and those that had received no prior treatment. There was also no observable difference in the response to treatment between children from either group with different forms of amblyopia (strabismic, anisometropic, etc.). Finally, examination of the longitudinal acuity scores across the 6 treatment sessions revealed no tendency for patients in the 2 treatment groups to respond to treatment at different rates.

CONTRAST THRESHOLD FUNCTIONS

The contrast thresholds for sinusoidal gratings were measured in each eye as a function of spatial frequency for 25 patients both before and after 6 treatment sessions. These measurements provide information on the relative threshold elevation in the amblyopic eye and also enable the limit of grating resolution acuity to be assessed. In general, the degree of amblyopic loss measured by this technique did not correlate in any simple manner with the degree of visual loss displayed on letter charts. Before treatment 19 out of 25 patients had a grating acuity of 30 cycles per degree or higher (mathematically equivalent to Snellen 6/6 or better). Only 2 patients had a grating acuity less than 20

cycles per degree (worse than 6/12). After treatment only 3 out of 25 patients showed a significant improvement in contrast thresholds or grating acuity. Of these, 2 were in the grey control group.

It was clear that contrast threshold function measurements do not clearly indicate the extent of the deficit as shown by letter charts, nor is it always a sensitive indicator of improvement in visual performance following treatment. As the issues involved here are rather complex, these findings will form the basis of a further publication (Howell, Mitchell, and Keith, in preparation).

STEREOPSIS

Stereoacuity was measured before and after the 6 treatment sessions in 52 of the patients. In agreement with a previous report¹³ measures of stereopsis obtained with the Frisby and Titmus test showed good correspondence, but those measured with the TNO test showed consistently poorer scores. Stereoacuity improved significantly in 8 out of 28 patients who were in the grating group and 5 out of 24 patients in the grey control group. In all but 1 case the final stereoacuity was better than 100 seconds, with 6 cases having clinically normal acuity of 40 s or better. There was no significant difference in improvement between the 2 groups. In all cases in which there was improvement fixation was central or parafoveal, with either no deviation or a squint angle less than 5°, and there had been no surgical intervention. These findings will be described in greater detail in a later publication.

FOLLOW-UP

Twenty patients from the RCH returned for a review examination between 1 and 9 months after cessation of treatment. The visual acuity was con-

sidered unchanged if there was not more than 0.1 log unit difference from the score at the end of treatment. Among those patients treated with gratings 8 were unchanged, 2 had deteriorated almost to the level which existed prior to initiation of treatment, and only 1 had improved (by 0.2 log unit). Of the 9 patients in the grey control group 7 remained unchanged and 2 had deteriorated to pretreatment levels. Fifteen of the patients attending the NVRIA were reviewed between 1 and 2 months after conclusion of treatment. Of 8 treated with gratings 7 were unchanged and 1 had deteriorated, while of the 7 in the control group 6 were unchanged and 1 had become worse. Thus there did not appear to be any obvious difference between the 2 treatment groups.

The comparable nature of the response of the patients to the 2 treatment regimens was also to be seen in the results from the 7 patients from the group treated with grey discs that were subsequently treated with rotating gratings. Six of these patients showed no further improvement in response to treatment with gratings, and only 1 patient improved by more than 1 line. This particular patient improved by the same amount (0.2 log unit) in response to the 2 treatment procedures.

Discussion

This study was primarily designed to assess the role of rotating gratings in the treatment of amblyopia by minimal occlusion. However, the results also provide insight into the value of minimal occlusion therapy as well as information on the relative effectiveness of different visual acuity tests for assessment of the degree of amblyopia. One control group was used, this group receiving as similar as possible management to the grating group but without exposure to the rotating gratings during treatment. As virtually all patients in both groups showed some improvement in vision with treatment, and the average improvement in the 2 groups were so similar, there are clearly other factors which are making significant contributions to the improvement. As these other factors were not controlled in this study, we can only speculate on their importance. Features of the treatment procedure that could contribute to the visual improvement include the period of weekly occlusion, which, including the time required for the tests of the visual function of the amblyopic eye, amounted to about half an hour; the intense nature of the visual tasks performed by the amblyopic eye during testing and treatment; and the need for concentrated eye-hand co-ordination during the treatment sessions. However, a number of other factors that might exert an

influence include the nonspecific improvements that occur with any type of treatment—therapist and possibly patient enthusiasm as well as the effect of practice in performing the various visual acuity tests. Finally, in addition to the factors already listed it is possible that some improvement might be attributed to the generalised arousal of the child on the occasion of each visit to the hospital or institute. Further studies are obviously necessary in order that these factors may be isolated and their relative contribution determined.

The grating test group in general showed similar magnitude of improvement in visual acuity to the control group. Inspection of Table 1 indicates that the average improvement on all 6 acuity scores of the patients in the subgroup treated with gratings and having an initial acuity better than 6/60 was marginally greater than that of the patients in the control group. However on only 1 measure, the distance full-line acuity scores on the Bailey-Lovie chart, was this very small difference statistically significant by both a Student *t* test and the non-parametric Mann-Whitney U test. On this measure the grey control subgroup improved by 0.08 log unit (0.8 of a line) and the grating subgroup by 0.15 log unit (1.5 lines) giving a relative improvement of 0.07 log unit (0.7 line). This difference was not seen so clearly in the part-line and single-letter scores, where the grey control group scores were larger. In the 6/60 minus subgroup the general magnitude of improvement was much greater (0.48 log unit average across all tests for the grey group) but again with no significant difference between the grating and the grey group.

Active stimulation of the amblyopic eye by intense visual stimuli has been advocated in the past for the treatment of amblyopia.¹⁴⁻¹⁶ The Cambridge group also regarded the visual stimuli received during treatment as an essential factor contributing to the improvement observed in their patients. It was thought that the series of rotating gratings acted as particularly potent stimuli for cells in the visual cortex receiving input from the amblyopic eye. However, since the improvement in the vision of the 2 groups of patients in our study was so similar, it would appear that aspects of the treatment procedure other than the rotating gratings were responsible for most of the improvement that was observed. However, the possibility still remains that stimulation of the amblyopic eye with rotating gratings produces a very slight further improvement in vision in some patients over that produced by the other aspects of the minimal occlusion therapy.

The visual improvement in our patients was not quite so marked as that reported by Campbell *et al.*⁶ who found that 73% of their patients achieved 6/12

vision or better on conventional test charts, while only 28% of our treated patients reached this level on the Bailey-Lovie chart. However, some of the discrepancy between the 2 findings can be accounted for by the differences between the visual acuity tests that were employed in the 2 studies. As emphasised earlier, the measured acuity of the amblyopic eye differed according to the visual acuity test that was administered. In general, the measured acuity was best for single letters and lowest with the Bailey-Lovie chart. Conventional test charts, as already discussed, are characterised by both an unequal number of letters on each line and an unequal relative spacing between letters. Although there are a greater number of letters towards the bottom of the chart, the spacing is relatively larger, so that contour interaction effects are reduced on these lines in comparison with lines in the middle of the chart, where these effects are greatest. Consequently an amblyopic eye will tend to perform better on conventional charts than on those such as the Bailey-Lovie chart, where some attempt has been made to maintain contour interaction effects constant on each line.

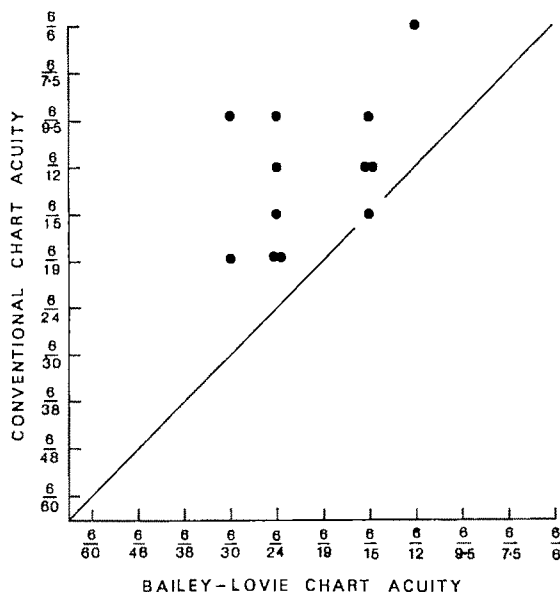


Fig. 7 The acuity scores of 12 amblyopic patients measured on both the Bailey-Lovie chart and a conventional test chart conforming to the British standard (BS 4274, British Standards Institution, 1968). To aid comparison the divisions on the 2 axes conform to the letter sizes on the Bailey-Lovie chart. The diagonal line indicates equal acuity on the 2 charts. Note that, with the exception of 1 patient, scores on the conventional chart indicated better acuity than those on the Bailey-Lovie chart.

This point is graphically illustrated in Fig. 7, which shows the relationship between the acuity scores obtained on conventional and Bailey-Lovie charts for the 12 patients on whom both these measures were made. With the exception of 1 child, on whom the scores were identical, measures obtained on the former chart were consistently better by several lines and in 1 child by 5 lines (6/6 versus 6/30). On the other hand the discrepancy between the scores of these 12 patients on the conventional acuity chart and on single-letter acuity tests were not so marked. In 5 cases the acuities were the same, and in 7 the single-letter acuity was better by about 2 lines. In agreement with this latter finding the final single-letter acuity was 6/12 or better in 78% of our patients, a figure comparable to the proportion of patients (73%) treated by Campbell *et al.*⁸ that attained this acuity on conventional test charts.

Although the patients in this study were heterogeneous for the type of amblyopia, there was no observable difference in the response to treatment between patients having different types of amblyopia. This was so despite the fact that the initial vision was quite different for the various types, being worst among strabismic amblyopes, relatively good (6/19+) for anisometropic amblyopes, and best (6/12+) for the small number of subjects with no observable accompanying peripheral defect.

In addition to the level of acuity eventually attained in response to treatment with rotating gratings Campbell *et al.*⁸ also placed some emphasis on the increase in the rate of improvement of vision over that achieved by minimal occlusion therapy. To produce the same degree of visual improvement (to 6/12) achieved after only 3 weekly treatment sessions with rotating gratings 13 weeks of occlusion for 20 minutes each day were required. By contrast we observed no consistent difference in the rate of visual improvement among the members of the 2 groups treated with gratings or with grey disc. Another feature of the rotating grating treatment mentioned by Banks *et al.*⁴ and later by Banks and Barnett¹⁷ was the improvement that tended to occur after treatment was discontinued. This was not consistently observed in the present study. While 1 patient from the group treated with gratings and 3 patients from the grey control group improved in visual acuity by 0.1 log unit, only 1 patient (treated with gratings) improved by more than this amount (0.2 log unit). Thus the 2 groups did not differ noticeably after cessation of treatment.

The work of the Cambridge group has stimulated renewed interest in the use of minimal occlusion in association with intensive visual tasks and concurrent visually guided motor activity in the treatment of amblyopia. We have confirmed their

findings that reasonably substantial visual improvements can be produced by this treatment (although we cannot exclude that this is not just due to practice), which is possibly preferable to long periods of unsupervised occlusion in the older child, and in cases of latent or manifest nystagmus which are in fact aggravated by occlusion. However, we have found that overall the rotating grating patterns that were viewed during treatment made little or no contribution to the improvement in vision or to the rate at which this occurred.

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Lack of positive results of a physiologically based treatment of amblyopia

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SUMMARY Recent reports have described marked improvement of visual acuity in amblyopic eyes of young children following monocular exposure to square-wave gratings presented at a variety of spatial frequencies and orientations for as little as 7 minutes. We sought to confirm and expand on these investigations, with emphasis on single-session results. Sixteen juvenile and 11 adult amblyopes and 26 control subjects were used. Visual acuity was determined before and after a 7-minute stimulation period using an E-chart that controlled for contour interaction. The 50% visual acuity threshold corrected for guessing was computer calculated by probit analysis. Results show that frequency, range, and magnitude of changes (either increases or decreases) in visual acuity following stimulation were approximately the same ($< \pm 10\%$ Snell-Sterling) in both amblyopic and control groups. These findings suggest that brief exposure to the grating patterns had little if any beneficial effect on visual acuity in amblyopic eyes.

The normal visual environment consists of objects of various orientations, contrast levels, and spatial frequencies. The cytoarchitecture and neuronal circuitry of the visual cortex, at least in cats and monkeys, are designed to analyse such sensory information,¹⁻⁶ and similar mechanisms are believed to underlie human form vision.⁶⁻⁹

Amblyopia, affecting approximately 2% of the general school age population,¹⁰ is a condition in which visual acuity is reduced in the absence of ocular or neurological disease, structural abnormalities of the eye or visual pathways, and uncorrected refractive error. If, as is commonly believed, amblyopia is a disorder primarily affecting the visual cortex, then perhaps pools of cortical neurons could be activated (or 'reactivated' or 'exercised') by receiving optimal visual stimulation, and this in turn might result in improved vision function in the amblyopic eye. Treatment for amblyopia using such a rationale, that is, gratings of a wide variety of spatial frequencies and orientations, has recently been proposed,¹¹ and preliminary positive results with only very brief periods of monocular treatment have been reported in young amblyopes.¹¹⁻¹⁵

We sought to confirm and expand upon these

initial grating treatment results using a carefully controlled method of obtaining visual acuity, as most of those authors' patients showed marked improvement of visual acuity in the amblyopic eye after only one 7-minute session. Furthermore, we performed several critical control experiments to help in interpretation of our results in juvenile and adult functional amblyopes.

Materials and methods

A device similar to the CAM vision stimulator¹¹⁻¹⁵ was used to stimulate the patient's amblyopic (or nondominant) eye. Square-wave gratings (on Kodalith paper) having a spatial frequency of either 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, or 32.0, (and frequently 64.0) cycles per degree (equivalent to visual acuity levels of approximately 20/1200 to 20/10) were viewed for 1 minute each (some patients reported seeing a uniform, grey field when the higher spatial frequency gratings were used). Grating contrast was high (about 90%) in order to minimise effects of reduced contrast sensitivity¹⁶⁻¹⁹ and abnormally rapid visual adaptation²⁰⁻²³ believed to be present in some amblyopic eyes. The circular field subtended 8 degrees at the eye and slowly turned at a rate of 1 revolution per minute; this, all orientations, and a wide range of grating spatial frequencies were available to stimulate the amblyopic eye. Further,

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a field of this size allows for stimulation of the central retina (including the fovea and eccentric fixation locus) in the presence of increased amblyopic drift,²⁴ strabismus-induced saccadic intrusions,²³ and small (<2 degrees) magnitudes of eccentric fixation.

The gratings were placed perpendicular to the estimated visual axis of the patient's viewing eye, and fixation distance of 57 cm was maintained throughout the 7-minute session. The patient was instructed to fixate accurately the centre of the grating and to try to keep the stripes as clear as possible. The experimenters constantly monitored the patient's eye position by gross visual observation and continually asked the patient questions about the grating, such as orientation and changes in clarity and contrast, in order to maintain a high level of attention to the task and as accurate as possible focus on the stripes. This was especially critical in young children, where games were also invented as needed to keep the patient's attention on the grating. A Plexiglass cover over the stimulating field, as used by others,¹¹⁻¹⁵ on which their young amblyopes drew pictures and played games during stimulation periods, was purposely not incorporated into our apparatus, as it was our belief that the patient's hand, arm, and crayon would frequently obscure part of the small stimulating field. Moreover, it is difficult to keep a small child at a relatively long, fixed distance (in order to know precisely the effective spatial frequency of the stimulating field) while drawing, as children typically move close (with distance depending upon such factors as arm length, visual acuity, and attention) to the material of interest. Each patient received the grating stimulation individually.

Visual acuity, with refractive error corrected and the nontested eye fully patched, was first measured in the dominant eye of most patients and then in the amblyopic eye before and after a single 7-minute session. Visual acuity was assessed by having the patient either specify verbally or indicate with a large hand-held E the orientation of the 8 Es on each test card (75 ft-candles (800 lux) illumination) located 10 ft (3 m) away²⁵ (Fig. 1). With this test target configuration, contour interaction effects were maintained constant,²⁶⁻²⁸ thus reducing variability of visual acuity measures in amblyopic eyes, as may be particularly prominent when conventional Snellen whole-chart or whole-line acuity is measured.²⁹ Test letter sizes ranged from 20/277 to 20/9, but not all test letter sizes were required to obtain an acuity measure; test time per trial was 10-20 minutes. Per centage correct at each letter size, from the largest letter size to the smallest, was plotted to obtain an initial estimate of results (Fig.

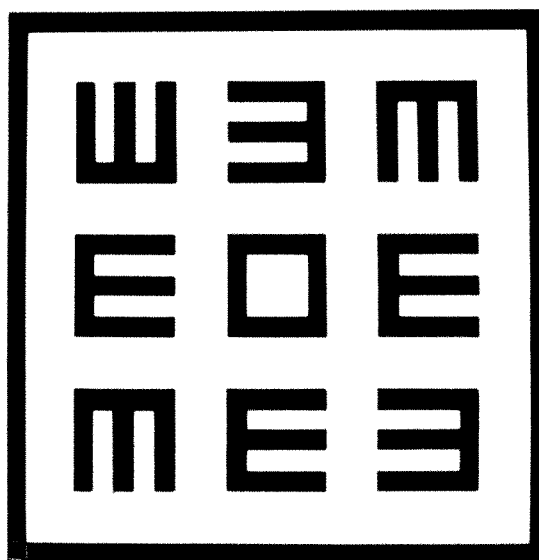


Fig. 1 E chart used for measuring visual acuity with control for contour interaction.

2). Then visual acuity, both Snellen and Snell-Sterling,³⁰ was determined by probit analysis³¹ via a minicomputer.

Juvenile and adult amblyopes, as well as several controls, were used in our study (see Table 1). The first control group consisted of normal adults receiving no stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on normal variability of acuity measures in adults by our method without influence of grating stimulation and concentrated fixation. The second control group consisted of normal adults receiving grating stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on influence of grating stimulation, if any, in eyes of normal adults. A third control group consisted of normal children receiving no grating stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on normal variability of acuity measures in children by our method without influence of grating stimulation and concentrated fixation. The fourth control group consisted of normal children receiving grating stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on influence of grating stimulation, if any, in eyes of normal children. A fifth control group consisted of nonamblyopic children with a diagnosis of learning disability and associated hyperactivity receiving grating stimula-

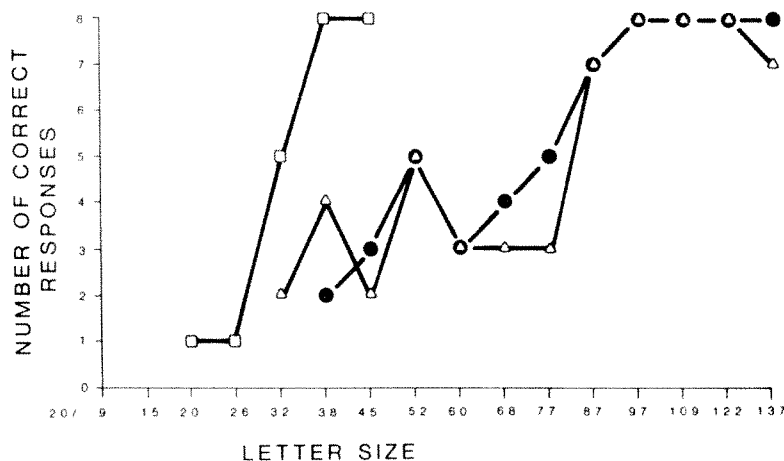
Table 1 Clinical and experimental data on patients

Patient	Age	Strabismus	V _{AB}	V _{AA}	ΔV_A (% S-S)	Patient	Age	Strabismus	V _{AB}	V _{AA}	ΔV_A (% S-S)
<i>Amblyopic children: grating stimulation</i>						33	22	XT	20/95-6	20/76-0	-9.5
1	6	ET	20/181-4	20/163-2	-4.2	34	24	ET	20/95-8	20/110-1	+6.1
2	6	ET	20/162-9	20/162-6	-0.1	35	28	NO	20/51-2	20/54-9	+2.5
3	8	NO	20/132-8	20/136-3	+1.1	36	23	ET	20/45-1	20/43-3	-1.2
4	9	ET	20/99-5	20/97-2	-1.0	37	21	NO	20/43-2	20/34-4	-7.5
5	13	ET	20/76-4	20/72-3	-2.3	38 ^d	34	NO	20/26-7	20/31-0	+5.5
6	7	ET	20/53-2	20/55-7	+1.7				20/26-5	20/28-3	+1.6
7	8	ET	20/50-6	20/48-8	-1.3	39 ^d	27	NO	20/175-6	20/168-5	-1.6
8	8	ET	20/45-7	20/38-2	-5.5				20/162-5	20/159-0	-0.9
9	7	ET	20/38-3	20/50-6	+8.9				20/180-6	20/171-8	-1.9
10	10	ET	20/28-4	20/24-8	-3.1				20/158-5	20/163-6	+1.3
11	7	ET	20/23-2	20/24-2	+0.9	40 ^e	39	ET	20/30-4	20/30-6	+0.1
12 ^a	9	ET	20/65-7	20/67-0	+0.8				20/31-0	20/28-1	-2.4
			20/63-9	20/65-0	+0.7				20/34-3	20/29-6	-3.8
			20/61-1	20/66-5	+3.3				20/23-6	20/22-9	-0.6
13 ^a	15	NO	20/48-3	20/45-9	-1.7				20/24-6	20/27-6	+2.5
			20/40-7	20/35-0	-4.4				20/27-3	20/27-9	+0.5
			20/28-5	20/26-0	-2.1	41 ^f	34	ET	20/61-3	20/46-3	-9.9
			20/12-4	20/14-8	+2.3				20/50-2	20/49-7	-0.4
14 ^b	12	NO	20/26-8	20/24-6	-1.8				20/46-5	20/39-0	-5.6
15 ^b	10	ET	20/23-9	20/18-7	-4.6				20/42-8	20/39-2	-2.7
16 ^c	13	ET	20/22-8	20/21-2	-1.5				—	20/33-3 ^g	—
<i>Amblyopic children: grey field stimulation</i>						<i>Amblyopic adults: no stimulation</i>					
17	9	ET	20/30-2	20/28-7	-1.3	42 ^h	27	NO	20/169-2	20/160-3	-2.2
18	8	XT	20/113-2	20/122-9	+3.6				20/181-7	20/167-8	-3.1
<i>Normal children: grating stimulation</i>						43 ^h	22	XT	20/74-8	20/71-6	-2.0
19	11	NO	20/14-9	20/18-7	+3.5				20/68-1	20/66-0	-1.2
20	12	NO	20/16-5	20/14-6	-1.2	<i>Normal adults: grating stimulation</i>					
21	9	NO	20/24-5	20/23-2	-1.1	44	25	NO	20/14-6	20/12-2	-2.3
22 ^e	10	NO	20/37-8	20/32-5	-4.1	45	31	NO	20/6-4	20/12-8	+6.3
23 ^e	8	NO	20/117-3	20/139-7	+7.6	<i>Normal adults: no stimulation</i>					
<i>Normal children: no stimulation</i>						46	23	NO	20/21-5	20/11-1	-9.7
24	5	NO	20/15-9	20/18-2	+2.1	47	26	NO	20/6-1	20/10-2	+4.0
25	6	NO	20/23-4	20/20-8	-2.3	<i>Organic amblyopic adults: grating stimulation</i>					
<i>Children with learning disability: grating stimulation</i>						48	19	NO	20/113-7	20/114-8	+0.4
26	9	NO	20/15-2	20/15-3	+0.2	(nystagmus)					
27	9	NO	20/16-0	20/10-7	-5.1	49	45	NO	20/98-7	20/104-0	+2.6
28	13	NO	20/17-6	20/17-5	-0.1	(histoplasmosis)					
29	8	NO	20/18-5	20/19-5	+0.9	50	60	NO	20/77-5	20/63-4	-8.0
30	8	NO	20/18-7	20/13-3	-5.0	(optic atrophy)					
<i>Amblyopic adults: grating stimulation</i>						51	69	NO	20/35-3	20/31-7	-2.9
31	46	NO	20/170-2	20/163-2	-1.8	(diabetes)					
32	25	ET	20/110-4	20/138-2	+9.8	52	67	NO	20/30-5	20/34-2	+3.0
						(cataract)					
						53 ⁱ	16	XT	20/70-0	20/67-5	-1.4
						(ptosis)					

a = Tested during orthoptics therapy; sessions separated by 2 weeks. b = Former amblyopes that had previously received orthoptics therapy; nearly normal visual acuity present. c = Uncorrected refractive error. d = Tested on consecutive weekly sessions. e = Tested on 6 consecutive daily sessions. f = Tested on 5 consecutive weekly sessions. g = Visual acuity following a weekend of stimulation 5 times per day. h = Tested on 2 consecutive sessions within a 1 hour period. i = Probable stimulus deprivation component to amblyopia resulting from severe congenital ptosis operated on at ages 5 and 12.

ET = Esotropia. XT = Exotropia. NO = None.

Fig. 2 Plot of letter size versus number of correct responses. Symbols: ● = Amblyopic eye before grating stimulation, △ = Amblyopic eye after grating stimulation, □ = Nonstimulated dominant eye. Computer-calculated 50% visual acuity threshold, corrected for guessing, in the amblyopic eye is 20/65.7 before stimulation and 20/67.0 after stimulation; it is 20/31.8 in the dominant eye. Note sharp fall-off of responses in dominant eye in contrast to gradual fall-off in nondominant (more amblyopic) eye as letter size decreases.



tion between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on variability of acuity measures in children, in whom variability of measures in this selected group might be expected to be unusually high, by our method. The sixth control group consisted of amblyopic children receiving grey-field stimulation in place of the gratings between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here separated effects of concentrated fixation from effects of grating stimulation. A seventh control group consisted of amblyopic adults receiving no stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information on normal variability of acuity measures in amblyopic adults without influence of grating stimulation and concentrated fixation. The last control group consisted of adults with reduced visual acuity resulting from ocular disease, who received grating stimulation between 2 consecutive determinations of visual acuity separated by 7 minutes. Results here provided information that would allow comparison between effects of grating stimulation and concentrated fixation on variability of acuity measures in functional and organic amblyopes.

Patients were recruited from the refraction and orthoptics clinics. All received a thorough examination of vision, including determination of refractive error (noncycloplegic), binocular status, and ocular health. No patients in the experimental groups had ocular or neurological disease or nystagmus. There were approximately an equal number of amblyopes whose condition could be attributed primarily to either strabismus or anisometropia. Most patients had esotropia. No patients had eccentric fixation greater than 3 prism dioptres as determined by visuoscopy. Most (about 70%) patients had astig-

matism, of 0.75 dioptre or greater, generally of either the mixed or compound myopic variety.

Results

Results are presented in Table 1. In general the use of the gratings had little if any effect on improving distance visual acuity in amblyopic eyes. Changes of visual acuity (either increases or decreases) with respect to magnitude, direction, and frequency were approximately the same in the amblyopic and control groups ($< \pm 10\%$ Snell-Sterling). In fact it is doubtful whether most of the computed visual acuity changes following brief grating stimulation could have been detected by conventional clinical procedures, that is, without use of a computer and with the use of whole-chart or whole-line Snellen measures, as they were generally so slight.

Discussion

We were unable to confirm the positive findings of Campbell and colleagues.¹¹⁻¹⁵ We believe that at least 3 factors are responsible for differences in results. The first and perhaps most important factor is method of measuring visual acuity. Campbell and colleagues employed Snellen, linear Sheridan Gardiner, and single Sheridan optotypes, and thus were not consistent in the use of a single procedure to obtain visual acuity in all patients. Further, with their method they did not control for contour interaction effects,²⁶⁻²⁸ a critical factor for accurate and repeatable determination of visual acuity in amblyopic eyes. We were consistent in our method²⁵ of determining visual acuity, which controlled for contour interaction by maintaining interletter separation with a fixed proportion of letter size.

The second factor is the use of controls. Although

Campbell and colleagues suggested that control studies should be conducted before widespread use of this technique is adopted,¹¹ and further stated that grey-field stimulation produced only slight improvement of visual acuity in some amblyopic patients,¹⁴ they did not provide quantitative findings for their controls. We provided quantitative findings in our controls and found that changes of visual acuity in controls were similar to those for our 'treated' amblyopic group, suggesting lack of a positive effect of the gratings on improving visual acuity in the amblyopic eyes of our patients. Changes of visual acuity noted in our control groups ($< \pm 10\%$ Snell-Sterling) could be attributed to normal variability of visual acuity. Further, small improvements of acuity could be attributed in part to practice effects, well known to vision care practitioners and reported in the literature.³²⁻³⁵ We believe that similar arguments apply to our experimental group. If we had obtained positive results in our amblyopes, an increased number of experimental and control subjects and additional control groups would have been essential on our part to factor out effects of short-term fixation training, short-term occlusion effects, practice effects, and/or normal variability of visual acuity from effects directly related to grating stimulation alone. While our sample size was not large, we believe that careful measures on a group of this size are preferable to testing a large group in the absence of appropriate controls and measurement techniques. Further, the consistent results we obtained do not demand that sample size be increased to provide a convincing argument.

The third factor is a history of previous occlusion therapy. In Campbell and colleagues' group 75% of the subjects had past history of partially successful occlusion therapy, while in our group only 33% did. One could speculate that patients having had some previous success with occlusion therapy might respond more favourably and rapidly to short-term occlusion during which motor activity is encouraged than those never having had such occlusion experience. Further, that favourable results in young amblyopes may follow brief periods of daily occlusion has been reported.³⁶ However, none of our amblyopes with history of occlusion therapy had significant gains in acuity after stimulation, though gains were the rule.

Other aspects related to the experimental methods deserve comment. We had patients view gratings without the addition of eye-hand sensory-motor feedback, as this was the procedure originally described.¹² This 'passive' procedure allows one to test those authors' original hypothesis on 'exercising' or 'activating' cortical neurons by viewing gratings

at a variety of spatial frequencies and all orientations in the purest form, that is, free from other factors such as eye-hand interactions, presence of hand and crayon in the visual field blocking the grating stimulus, presence of printed letters and game form in the field providing additional stimulus patterns, and the tendency of young children to move close to the grating during active visual tasks and thus change fixation distance and effective stimulus spatial frequency, since the 'game' surface was on top of the grating stimulus. All these became additional factors that one must consider potentially important during the stimulating period and which make results difficult to interpret when adequate controls are not provided. Further, we had individuals view the gratings at a carefully monitored and fixed distance perpendicular to the stimulating surface; in contrast, they had 2 patients playing games while viewing the grating, at least some of the time, at an oblique angle, thereby changing its effective size, shape, and spatial frequency.

Our negative results do not stand alone. Recent papers have reported similar results.^{37,38} With few exceptions an informal survey conducted by the first author of several clinical researchers testing the grating treatment also provided negative results. Lastly, lack of sustained effect of the treatment on visual acuity with concurrent lack of effect on the visually evoked response in 1 young amblyope has recently been reported.³⁹

In conclusion, under our test conditions the grating treatment appeared to have little effect on distance visual acuity in the amblyopic eyes of our juvenile as well as adult patients. We believe that conventional orthoptics procedures for the treatment of amblyopia, such as partial or total occlusion, training in monocular and binocular skills, and eye-hand co-ordination activities guided by the amblyopic eye, should not be discarded or minimised in the treatment of amblyopia until new techniques tested in amblyopes with proper controls and resulting in high success rates, independently confirmed by other laboratories, are available.

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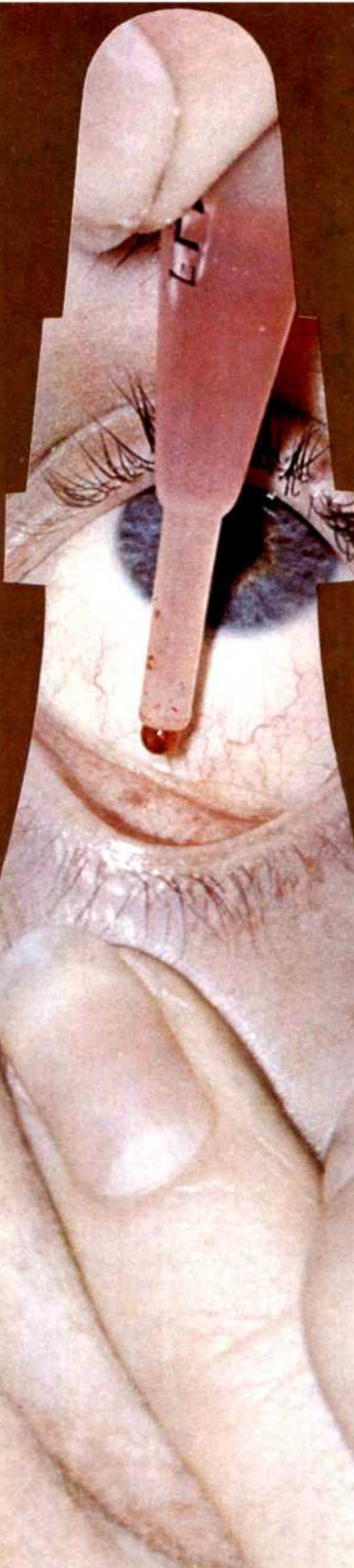
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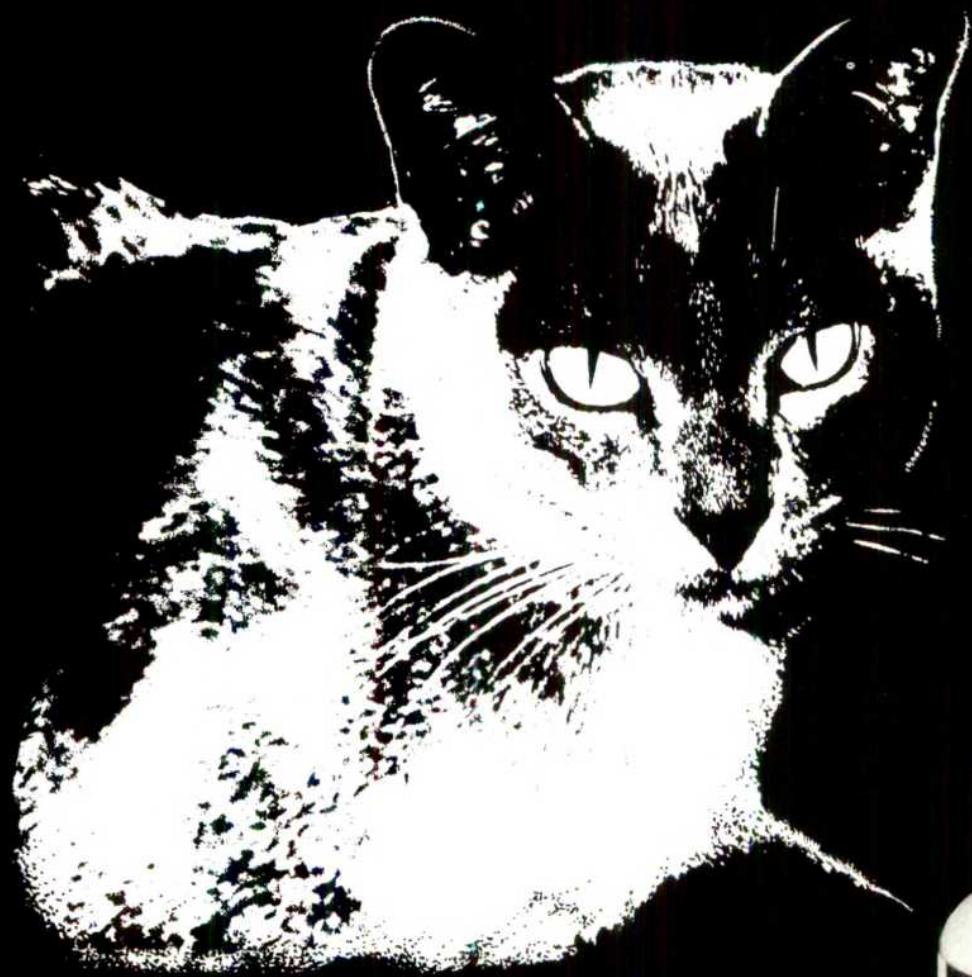
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Loss of contrast sensitivity following contusional eye injury

Y. CANAVAN AND D. B. ARCHER

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SUMMARY Contrast sensitivity was evaluated in 95 patients who regained a visual acuity of 6/6 following a contusional injury to one eye. The injuries occurred 2 to 12 years prior to examination. A book of printed sinusoidal grating patterns of varying contrasts and spatial frequencies was used, and 15 patients were found to have a significant difference in contrast sensitivity between injured and uninjured eye. Eight patients had abnormalities of the media or fundus, and in 2 patients amblyopia was probably a factor. Five patients had a defect in contrast sensitivity in their injured eye, although no structural abnormalities could be detected on full clinical examination. Alterations in contrast sensitivity appeared to be a sensitive indicator of functional abnormality in eyes which appeared normal on ophthalmoscopy and other clinical investigations.

Contrast sensitivity is an important and measurable parameter of visual function, although its anatomical and physiological basis has yet to be fully explained. Loss of contrast sensitivity may occur in certain ocular disorders where there is no detectable alteration in visual acuity or field and where no structural abnormalities of the eye can be identified. Bodis-Wollner¹ described loss of contrast sensitivity in patients with intracranial lesions and normal visual acuity, and Sjöstrand and Frisen² noted significant loss of contrast sensitivity in patients with macular disease accompanied by only minimal loss of central visual functions. Patients with amblyopia³ or myopia and astigmatism⁴ may also demonstrate loss of contrast sensitivity.

Arden,⁵ in 1978, described a simple technique for the clinical measurement of contrast sensitivity. He transferred a selection of 6 sinusoidal grating patterns of varying contrast and spatial frequency on to paper and produced a book which could be used rapidly and easily in the clinical evaluation of patients. The book was loose-leaf and each page was enclosed and protected by a plastic folder. Each text contained six sheets exhibiting sinusoidal grating patterns (plates 2-7), each sheet illustrating a grating of specific spatial frequency and designed to be read at 57 cm. The contrast on each plate increased progressively from subthreshold (uniform

grey appearance) to higher and higher contrast areas. An arbitrary scale placed at the side of each plate facilitated the numerical recording of the patient's threshold position.

Arden and Gocukoglu⁶ reported on 57 patients with retrobulbar neuritis (with or without other signs of multiple sclerosis) and found that the grating test highlighted abnormalities in contrast sensitivity in affected as well as unaffected eyes. They found that the abnormalities in contrast sensitivity thresholds compared favourably with electrophysiological testing as a technique to evaluate abnormalities of visual functions in such patients. Arden and Jacobson⁷ determined that the grating test was also of value in screening patients for glaucoma. Patients with glaucoma gave higher test scores than the normal range of the population and their loss of contrast sensitivity corresponded to the severity of the disease. Patients with ocular hypertension also demonstrated abnormal contrast sensitivity, further enhancing the effectiveness of this test as a screening procedure for glaucoma.

This paper reports an investigation of contrast sensitivity in 95 patients who suffered a contusional injury to the eye but who regained a visual acuity of 6/6 or better in the injured eye.

Materials and methods

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In a recent survey⁸ of 1063 patients with contusional (nonpenetrating) eye injuries of sufficient severity to

necessitate hospital admission it was found that 431 (40.5%) regained a visual acuity of 6/6 or better and were asymptomatic. Ninety-five of these patients were available for review, which was carried out between 2 and 12 years following injury. The patients' ages ranged from 10 to 75 years with an expected predominance in young adulthood.

Twenty-eight of the 95 patients were found to have no detectable structural abnormalities of the eyes on full ocular examination. Sixty-seven patients had significant structural alterations, of which the most common was recession of the anterior chamber angle. Fourteen patients had additional signs of anterior segment trauma including pupillary sphincter tears, iridodialyses, and localised lens opacities. Twelve patients were found to have lesions of the posterior segment of the eyes, the most common being retinal pigment epithelial alterations, small choroidal tears, or breaks in Bruch's membrane in the posterior and equatorial fundus.

Contrast sensitivity studies were carried out in this group of patients using the book of grating patterns and the technique advocated by Arden.⁵ Each eye was tested in turn, the other eye being covered. The injured and noninjured eyes were tested in a random fashion and appropriate reading spectacles used in those patients who required them. The patients were positioned at a table and the plates were scrutinised at a reading distance of 57 cm under indoor lighting conditions along with a near-by desk lamp (60 W bulb). The procedure was explained to the patient and one practice test was allowed. Each plate (2-7) was then read in turn, the plate being covered by a card which revealed only the subthreshold contrast, so that the patient appreciated only a uniform grey area. The card was then withdrawn slowly revealing higher and higher contrasts until the grating pattern became visible to the patient. The scale reading at this position was recorded, and the procedure was then repeated for each of the 6 plates and the scale readings for each plate indicating the contrast threshold summated to give a score.

The procedure was then repeated for the second eye. A difference of 10 or more between the scores for the 2 eyes was considered significant, indicating an abnormality of contrast sensitivity in the higher scoring eye.

Results

Of 95 patients reviewed 15 had significant loss of contrast sensitivity in the injured eye (i.e., a difference of more than 10 in the scores between the injured and uninjured eye). The score value difference between the 2 eyes ranged from 10 to 25+

Table 1 Analysis of 15 patients with significant loss of contrast sensitivity in injured eye

Patient number	Distance vision (with glasses if habitually worn)	Grating score difference between injured and uninjured eyes	Clinical examination of the injured eye
1	6/6	10.0	Normal
2	6/6	10.5	Normal
3	6/6	10.5	Normal
4	6/6	11.5	Normal
5	6/6	16.0	Normal
6	6/6	14.5	? Amblyopia
7	6/6	16.0	? Amblyopia
8	6/6	10.0	Lens opacities
9	6/6	10.0	Choroidal tears
10	6/6	10.5	Lens opacities
11	6/6	11.0	Sector optic Atrophy
12	6/6	11.5	Choroidal tears
13	6/6	24.0	Repaired retinal Detachment
14	6/6	24.5	Optic disc Pallor
15	6/6	25.0	Choroidal tears

(Table 1). Patients 1 to 5 showed significant loss of contrast sensitivity in the injured eye, though they were asymptomatic and had a corrected visual acuity of 6/6 or better. No physical abnormalities were detected on detailed ocular examination in this group to account for the discrepancy. Similar findings were noted in patients 6 and 7, but the interpretation of results was complicated, as patient 7 had a small intermittent divergent strabismus in his injured eye. The latter patient was unaware of the strabismus, and it was not possible to ascertain whether it predated the injury. Patient 6 also had a squint treated in childhood, but no significant deviation was noted on clinical evaluation.

Patients 8 to 15 were also found to have significant defects of contrast sensitivity in their injured eyes, but all patients in this group had structural abnormalities in the injured eyes which could have had an effect on contrast discrimination. Patients 8 and 10 had anterior and posterior cortical lens opacities respectively in the region of near-by iris tears or areas of iris atrophy. Three patients, 9, 12, and 15, had areas of retinal pigment epithelial atrophy or proliferation and areas of choroidal atrophy usually associated with 'choroidal tears'. In patient 9 only

a small localised area of retinal pigment epithelial and choroidal atrophy was present (Figs. 1, 2), but in cases 12 and 15 complex retinal pigment epithelial and choroidal degenerative changes were present in

the region of the posterior pole of the fundus (Figs. 3, 4). Patients 11 and 14 had significant optic atrophy. Patient 14 had moderate pallor of the optic disc, while in patient 11 the atrophic changes

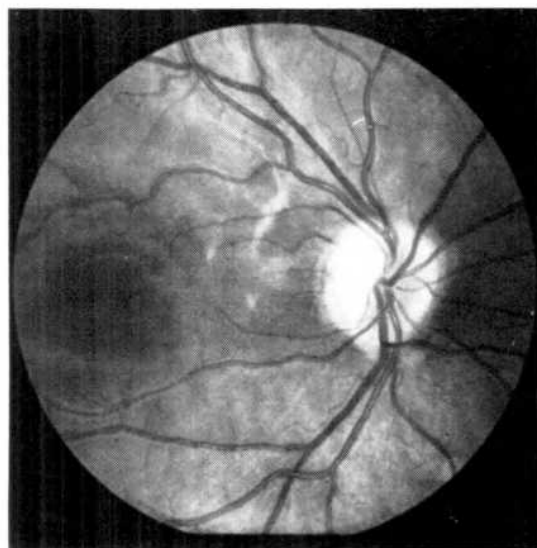


Fig. 1 Right fundus photograph of patient 9 showing 3 small areas of retinal pigment epithelial and choroidal atrophy involving the superior papillomacular region.

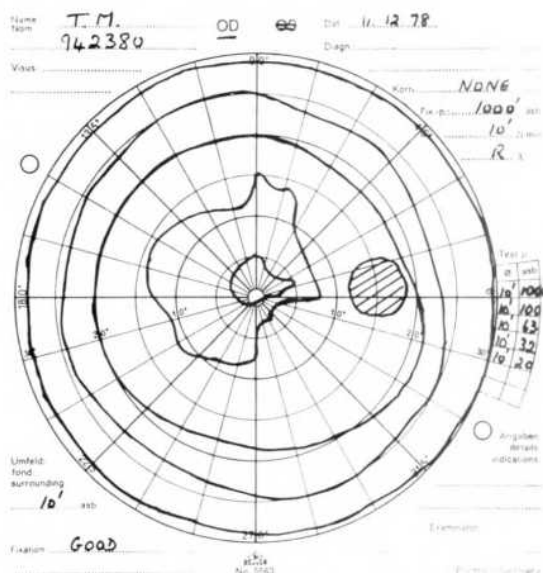


Fig. 2 Central visual field (Tübinger) of patient 9 shown in Fig. 1 demonstrating inferotemporal constriction of the visual field in the 5° and 10° isoptres.

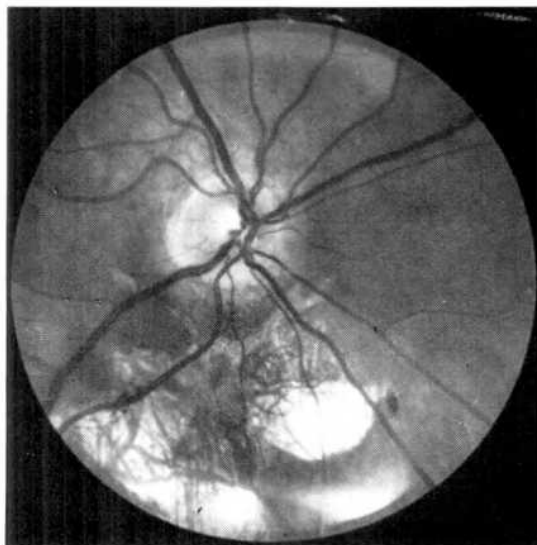


Fig. 3 Right fundus photograph of patient 12 demonstrating extensive patchy atrophy of the retinal pigment epithelium and choroid involving a sector inferior to the optic disc.

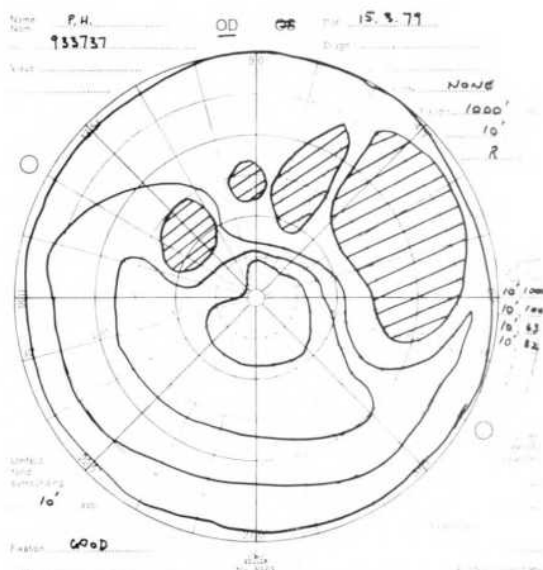


Fig. 4 Central visual field (Tübinger) of patient 12 shown in Fig. 3. Several large scotomata involve the right superior field. The fovea is spared.

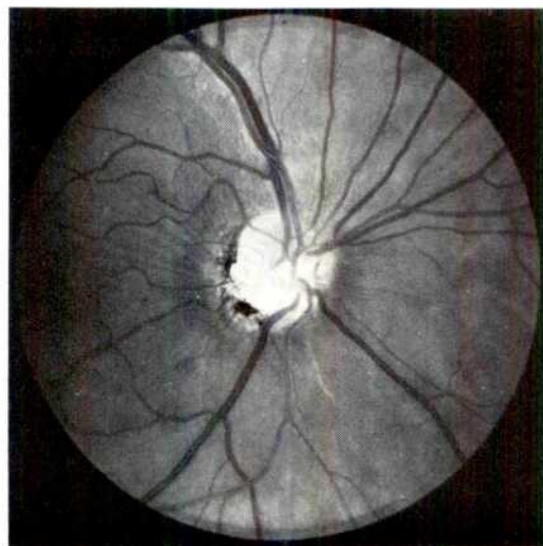


Fig. 5 Right fundus photograph of patient 11 demonstrating atrophy of the inferotemporal margin of the optic disc. Wrinkles in the internal limiting membrane radiate from the temporal part of the disc and nerve fibre striations are absent in the inferior retina.

were localised to an inferior sector of the right optic disc and associated with a superior altitudinal visual field defect (Figs. 5, 6).

Patient 13 developed a localised rhegmatogenous retinal detachment following injury and subsequently had an encirclement procedure to reattach the retina. This patient subsequently developed a diffuse retinal pigment epithelial disturbance over the superior half of the right fundus.

Discussion

Prolonged observation of a high-contrast grating reduces the visibility of a low-contrast grating of equal spatial frequency; however, sensitivity to gratings of other spatial frequencies remains unaffected.^{9,10} Campbell and Robson¹¹ suggested that within the nervous system there exist linearly operating, independent 'channels', selectively sensitive to limited ranges of spatial frequencies. Thus, one channel could be inactivated by adaptation while other functions remain unaffected. High spatial frequencies must be received at the fovea and the retinal periphery is probably receptive to lower frequencies. It is therefore likely that contrast sensitivity is affected in the presence of either peripheral or central retinal pathology.⁵ The ability to see low spatial frequency gratings is not limited by the refractive properties of the eyes. Difficulties in perceiving high frequency gratings, however, may

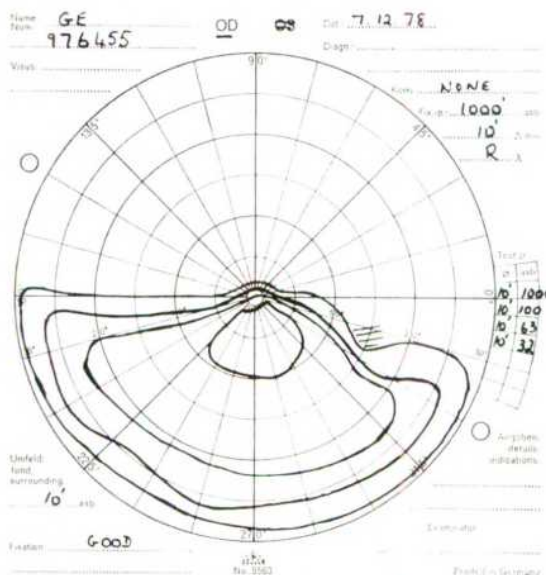


Fig. 6 Central visual field (Tübinger) of patient shown in Fig. 5. There is a superior altitudinal field defect, but the fovea is spared.

be attributable to a refractive error; therefore, difficulty with low frequency gratings identified patients suffering from a pathological condition.⁵ Until recently evaluation of contrast sensitivity has remained a laboratory investigation, most workers using oscilloscopic or televised displays. These methods were not suitable for clinical use, being expensive and difficult to transport. The development of a book of printed sinusoidal patterns has been a useful advance in testing contrast sensitivity in the clinical situation. The test is easily transported and rapidly performed. Patients in all age groups find the test relatively easy to understand, and a practice run using one plate is generally all that is required. Younger patients tend to see the grating pattern more quickly than older patients and hence have lower average scores. The test is therefore particularly useful in comparing right and left eyes of one patient and it is more difficult to compare results from patient to patient. There are certain variations in results depending on the observer's technique, and it is preferable that all tests in one study be carried out by one person, as was the case in this survey.

The Arden grating test in this particular investigation was reliable and reproducible, and only 2 false positive results occurred in 95 patients investigated. In 1 patient there was a marked and unexplained discrepancy in the scores between the 2 eyes, the uninjured eye having the higher score. A second

patient who also had a significantly higher score in the uninjured eye gave a definite history of squint and amblyopia in this eye which could have accounted for the discrepancy.

This investigation has established that the majority of patients who regained a visual acuity of 6/6 after contusional eye injury have no significant differences in contrast sensitivity in the injured and uninjured eyes. Fifteen patients, nevertheless, in this survey (14%) showed a significantly raised score (greater than 10) in the injured eye on testing with the Arden gratings. Eight of these patients had well-defined structural abnormalities of either the mediae or fundi which undoubtedly contributed to the defect in contrast sensitivity. In general the more severe the structural abnormality of the eye the more marked was the difference in contrast sensitivity score between the normal and injured eyes. Injuries associated with impaired visual acuity showed correspondingly severe diminution in contrast sensitivity in the affected eye.⁸

It is significant that 2 patients with early anterior and posterior cortical lens opacities secondary to trauma also showed loss of contrast sensitivity in the affected eye. This observation has been made previously by Arden⁸ and explains why patients with early lens opacities of any aetiology may complain of visual disturbances which seem out of proportion to a visual acuity of 6/6. In 2 further patients there were definite defects in contrast sensitivity in the injured eye where amblyopia was probably the contributory factor. Patients 1 to 5 are particularly instructive as they showed grating score differences of 10 to 16 between the injured and uninjured eyes in the presence of a normal visual acuity and absence of symptoms. The only structural abnormality detected in these patients was a mild degree of anterior chamber angle recession which

was not considered clinically significant. Contrast sensitivity testing therefore appears to be a sensitive indicator of functional abnormality in an eye judged to be normal using other clinical parameters.

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A 10-year survey of eye injuries in Northern Ireland, 1967-76

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SUMMARY Ocular injuries of sufficient severity to necessitate admission to the Eye and Ear Clinic, Royal Victoria Hospital, Belfast, were sustained by 1707 male patients and 325 female patients. Blunt injury occurred in 1063 eyes (49.2%), perforating injury in 1037 (48%), and intraocular or intraorbital foreign bodies in 181 eyes (8.4%). More than three-quarters of the patients (77.4%) were less than 36 years of age and 84% of all injuries occurred in males. Normal visual acuity (6/6 or better) was regained by 41.2% of the patients in whom the final visual outcome was known. The benefit of wearing seat belts in road vehicles and protective goggles in industry and sport should receive more publicity on radio and television and via poster campaigns. Compulsory fitting of laminated windscreens in all road vehicles is recommended. The vulnerability of children to ocular injury should be highlighted through the mass media, schools, and health centres.

Few general surveys of ocular injuries have been published in the ophthalmic literature in this century. This reflects the difficulties encountered in the accumulation of data relating to ocular injuries, particularly the inadequate initial documentation of eye injuries and visual functions and the failure to code accurately the diagnosis to facilitate data retrieval at a later date. These disadvantages may be further compounded by failure of patients to attend for review and the difficulties encountered in tracing injured subjects who often are part of a young and mobile population.

Garrow¹ in 1923 presented the first comprehensive survey of ocular injuries. He analysed 1000 consecutive cases of eye injury admitted to the Glasgow Royal Infirmary between 1908 and 1913 and emphasised the occupational nature of the majority of the eye injuries. In 1967 Yuasa *et al.*² reported a large series of patients (2484) with eye injuries. Many of these injuries, however, were minor in nature and the patient did not require admission to hospital. In 1968 Lambah³ reviewed over 1000 patients admitted to hospital with ocular injuries. This largely epidemiological survey concentrated on the cause of ocular injury. Johnston⁴ conducted a

selective survey of patients requiring treatment for eye injuries during the years 1965 to 1974 inclusive. He categorised the various types of injuries and highlighted the changing patterns of trauma during the years of the investigation. Most other studies relating to ocular trauma are limited to specific aspects of ocular injury such as the surgical management of perforating eye injuries and intraocular foreign bodies.⁵⁻¹⁶ Particular subjects such as the management of traumatic hyphaema have also been analysed in depth,^{17,18} and several studies compare the merits of medical or surgical treatment¹⁹⁻²¹ and analyse the indications for monocular or binocular patching²² and the use of urokinase.²³⁻²⁵

The present survey assesses the range and extent of eye injuries in patients admitted to the Eye and Ear Clinic, Royal Victoria Hospital, Belfast, over a 10-year period. The Eye and Ear Clinic provides general ophthalmological care for approximately 85% of the population of Northern Ireland and offers specialised ophthalmological facilities for the entire province. The population was 1 549 400 persons in 1972 (based on the 1971 census from the 51st Annual Registrar General's Report 1972). More than one-quarter (362 082 persons) live in the city of Belfast. Our analysis of the causes of ocular trauma attempts to identify areas in which prevention might be undertaken.

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Table 1 *Distribution of patients injured according to age and sex*

Age when injured (years)	Male			Female			All cases		
	No.	%	(N.I.)	No.	%	(N.I.)	No.	%	(N.I.)
0-	550	32.2	(31.2)	136	41.8	(28.6)	686	33.7	(29.8)
15-	649	38.0	(23.8)	102	31.4	(21.6)	751	36.9	(22.7)
30-	260	15.2	(16.4)	36	11.1	(16.2)	296	14.6	(16.3)
45-	204	11.9	(19.8)	33	10.2	(20.9)	237	11.6	(20.5)
65+	45	2.6	(8.8)	18	5.5	(12.7)	63	3.1	(10.7)
Total	1708* (1707)	99.9	(100.0)	325	100.0	(100.0)	2033* (2032)	99.9	(100.0)

*One individual had the same eye injured on different occasions. Proportion in brackets relate to the population of Northern Ireland (estimated 30 June 1972).

Materials and methods

2032 patients (2162 affected eyes) who sustained eye injuries requiring hospital admission between 1 January 1967 and 31 December 1976, were admitted to the survey. They were selected according to the diagnosis available through the medical records department (case notes with International Classification of Disease numbers (Eighth Revision) N870 and N921 for the years 1967 to 1976). Each patient was given a consecutive code number, and data relating to age, sex, annual and seasonal variation, eye injured, and aetiology of injury were recorded in addition to the nature and severity of the ocular injury and the final outcome. The information on each patient was transferred to punch cards for computer analysis.

Results

SEX

The distribution of ocular injuries by the sex and age of the patient demonstrates a clear difference in the incidence of ocular injury between the sexes (Table 1, Fig. 1). Although the male:female ratio of the population was 0.98, the male:female ratio for ocular injury was 5.25 which is a highly significant difference ($\chi^2=15.31$, $DF=4$, $P<0.001$ for males, and $\chi^2=24.80$, $DF=4$, $P<0.001$ for females). Females are particularly vulnerable in the first decade and beyond the fifth decade (Table 2). For males the greatest incidence of eye injury occurs in the second to fifth decades.

AETIOLOGY

In 1712 patients the cause of ocular injury was known. In the remaining 320 patients (15.7%) insufficient documentation made it impossible to identify the exact aetiology. Injuries occurring during

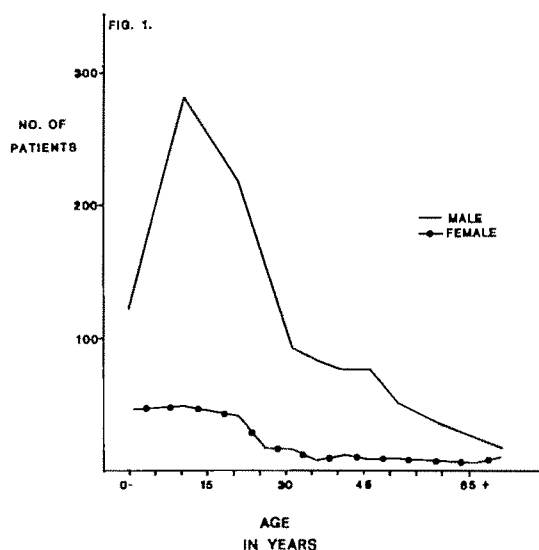


Fig. 1 *Distribution of patients injured according to age and sex.*

Table 2 *Distribution of injured patients according to age and male/female ratio*

Age when injured (years)	No. of cases	Male/female ratio
0-	429	3.62
11-	612	5.67
21-	425	6.34
31-	196	7.57
41-	167	8.28
51-	110	4.79
61+	93	3.22
Total	2032	5.25

play and sport to children were the most common aetiological factors (33.8%) with road traffic accidents (19.3%) and industrial injuries (15.4%) being next in frequency (Table 3 and Fig. 2). Together these latter 2 subgroups accounted for more than one-third of all injuries. Road traffic accidents were the most common cause of eye injury in females (35.9%), but for males injuries incurred during play and sport in childhood were the most common aetiological factors (33.9%).

INJURY AND AGE

The distribution of the number of eyes injured rather than individual patients injured is shown in Table 4 and Fig. 3. More than one-third (38.4%) of eye injuries in which the cause was known occurred in children under 16 years. In this age group over four-fifths (82.1%) of the injuries occurred to children engaged in play or sport and 7.7% resulted from accidents in the home. In older patients (16 years or older) approximately one-third (32.3%) of injuries were caused by road traffic accidents, with patients in the 16-25 year

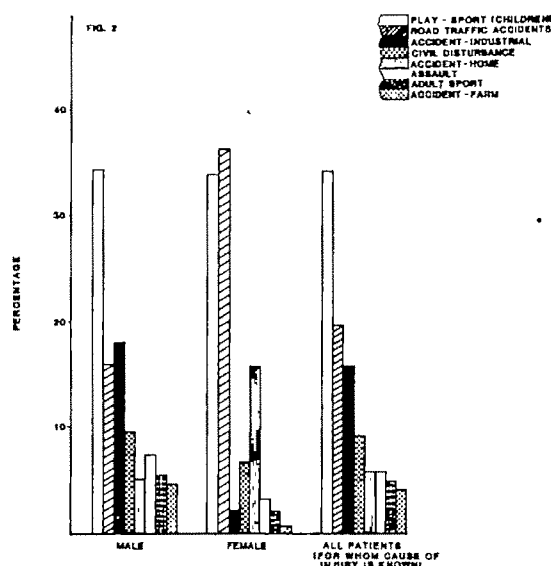


Fig. 2 Percentage incidence of ocular injury related to cause of injury and sex of patient.

Table 3 Distribution of injury by cause and sex

Cause of injury		Play and sport (children)	RTA†	Industrial accidents	Civil disturbance	Home accident	Assault	Adult sport	Farm accident	Total
Cases	No.	579*	330	262	156	117	117*	83	68	1713 (1712)
	%	33.8	19.3	15.4	9.1	6.8	6.8	4.8	4.0	100.0
Male/female ratio		5.09	2.24	42.83	7.21	1.60	12.0	12.83	33.0	5.03

*One individual had both eyes injured but the cause was different on each occasion. †RTA = road traffic accident.

Table 4 Distribution of eye injury by cause and age at time of injury*

Cause of eye injury	Age when injured (years)										All cases
	Children (<16 years)				Adults (>16 years)						
	0-	6-	11-	Total children	16-	26-	36-	46-	56+	Total adults	
Road traffic accident	6	5	14	25	178	79	45	29	35	366	391
Civil disturbance	0	5	22	27	71	35	26	25	8	165	192
Adult sport	0	0	5	5	41	20	8	6	4	79	84
Play and sport (children)	126	224	229	579	7	0	0	0	1	8	587
Accident (home)	25	15	14	54	14	13	5	7	27	66	120
Accident (industrial)	0	0	9	9	109	64	46	33	12	264	273
Accident (farm)	0	1	1	2	11	7	15	14	19	66	68
Assault	0	0	4	4	51	27	12	11	18	119	123
Totals	157	250	298	705	482	245	157	125	124	1133	1838†

*This Table (and also Tables 5, 6, 7) counts the number of eyes injured and not the number of individuals injured.

†There were 324 eyes for which the cause of injury was not known; these are excluded from the above figures and from Table 5.

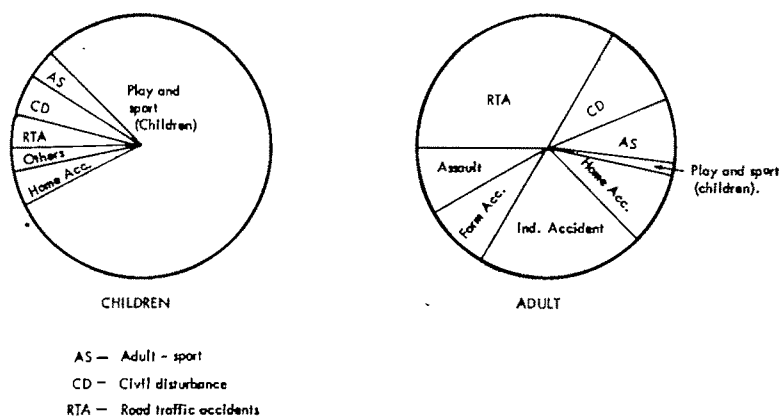


Fig. 3 Distribution of cause of ocular injury in adults and children.

age group accounting for nearly half (48.6%) of these injuries. Industrial accidents were responsible for 23.3% of ocular injuries with more than 41.3% of these occurring in the 16-25 year age group. Patients in the 16-25 year age group sustained more injuries in each aetiological category except those comprising accidents at home and on the farm. Patients age 56 years and over were most often involved in farming accidents.

SECULAR TRENDS

Comparison of the first and second quinquennials reveals a significant increase in the incidence of injury due to road traffic accidents ($\chi^2=29.28$, $DF=1$, $P<0.001$), civil disturbance ($\chi^2=63.02$, $DF=1$, $P<0.001$) and assault ($\chi^2=13.67$, $DF=1$, $P<0.001$). There is no significant trend for the

other aetiological groups (Table 5). In the second quinquennium 4 out of the 5 years exhibit a male:female ratio below the average of 5.25. This is most marked in 1972, which was the peak year for female injuries.

SEASONAL VARIATION

Examination of the winter:summer ratio reveals a variation by season for all aetiological groups of eye injury (Table 6). This is greatest in relation to civil disturbance, children at sport and play, and farming accidents. Adult sports injuries and accidents in the home or on the farm were more common during winter, while the other aetiological groups occurred more commonly during summer. Road traffic accidents do not vary significantly according to the season of the year (at the 5% level), but these

Table 5 Distribution of eye injury by cause and year of injury

Cause of eye injury	Admission year										Total eyes
	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	
Road traffic accident	23	28	26	23	42	56	58	44	49	42	391
Civil disturbance	0	0	16	7	18	45	27	25	20	34	192
Adult sport	10	9	6	8	7	13	4	10	10	7	84
Play and sport (children)	61	52	56	55	72	76	75	54	36	50	587
Home accident	9	14	8	13	15	14	10	8	16	13	120
Industrial accident	35	19	26	21	41	23	34	30	20	24	273
Farm accident	10	2	8	10	7	4	11	8	6	2	68
Assault	9	5	6	10	11	21	18	13	15	15	123
Total	157 (8.5)	129 (7.0)	152 (8.2)	147 (8.0)	213 (11.6)	252 (13.7)	237 (12.9)	192 (10.5)	172 (9.4)	187 (10.2)	1838* (100.0)
Male/female ratio	6.54	5.91	6.43	5.74	5.85	3.80	4.25	7.54	4.62	5.16	5.25

*See footnote to Table 4.

Table 6 *Distribution of eye injury by cause and month of admission*

Cause	Admission month												Total injuries	Winter/summer ratio*	χ^2 value†
	J	F	M	A	M	J	J	A	S	O	N	D			
Road traffic accident	29	25	34	29	30	30	25	38	25	38	36	52	391	1.21	3.50
Civil disturbance	8	14	10	9	20	20	26	33	10	23	14	5	192	0.63	10.08
Sport (adult)	7	12	3	3	6	8	4	10	8	8	8	7	84	1.15	0.43
Play and sport (children)	33	36	53	50	41	63	63	61	64	65	29	29	587	0.72	16.03
Home accident	8	10	13	13	12	7	4	11	11	14	9	8	120	1.07	0.13
Industrial accident	22	19	20	22	30	24	17	25	32	24	21	17	273	0.82	2.67
Farm accident	8	4	10	5	2	4	7	5	2	8	8	5	68	1.72	4.76
Assault	5	9	14	13	8	7	13	17	6	8	10	13	123	0.92	0.20
Total	120	129	157	144	149	163	159	200	158	188	135	136	1838	0.89	6.35

*Winter is defined as the first plus last quarters of same year; summer as the second plus third quarters.

†Calculated with 1 degree of freedom at 5% level = 3.84.

Table 7 *Distribution of 3 major causes of eye injury by year of admission*

Type of injury	Year of admission										Total eye injuries	χ^2 value*
	67	68	69	70	71	72	73	74	75	76		
Blunt	89	85	77	91	127	162	130	102	83	117	1063	60.28
Perforating	86	72	100	88	110	129	136	111	109	96	1037	33.18
Foreign body	14	12	21	16	18	21	28	15	16	20	181	11.11

*Calculated with 9 degrees of freedom at the 5% significance level = 19.675.

injuries increased in frequency during October, November, and December ($\chi^2=10.89$, $DF=3$, $P<0.05$).

INCIDENCE OF BLUNT AND PERFORATING OCULAR INJURY

There is a significant variation in the yearly incidence for both blunt ($\chi^2=60.28$, $DF=9$, $P<0.001$) and perforating ($\chi^2=33.18$, $DF=9$, $P<0.001$) types of injury, with the years 1971 to 1973 showing the peak incidence (Table 7 and Fig. 4).

Among those cases in which the cause of injury was known, blunt ocular injury occurred most frequently in the aetiological group of children at sport and play (38.7%). Road traffic accidents accounted for 30.2% of perforating injuries and accidents to children at sport or play for a further 24.1%. Industrial accidents caused 52.6% of intraocular or intraorbital foreign body injuries, the latter usually representing a through and through perforation of the globe.

VISUAL PROGNOSIS FOLLOWING INJURY

Examination of the outcome of all ocular injuries in which the final visual result was available revealed that more than two-fifths of eyes (41.2%) regained an acuity of 6/6 or better and a further

one-fifth (22.4%) achieved an acuity of between 6/7.5 and 6/12 (Table 8). However, approximately 1 patient in every 10 (12.3%) required enucleation of the injured eye. Of the 215 eyes enucleated 66

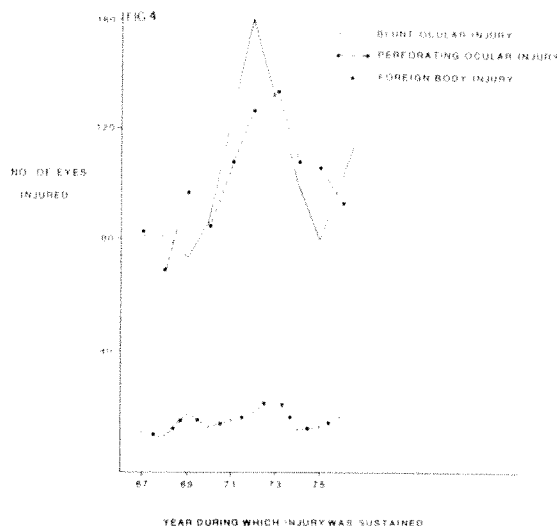


Fig. 4 Incidence of blunt, perforating, and foreign body injury according to year of injury.

Table 8 *Distribution of all eye injuries by final visual acuity*

Acuity	Eyes injured	
	No.	%
6/6 or better	721	41.2
6/7.5-6/12	391	22.4
6/18-6/36	157	9.0
6/60 or worse	197	11.3
Enucleation	215	12.3
No perception of light	67	3.8
Total	1748*	100.0

*There were 414 (19.1%) eyes for which the visual acuity was unrecorded or not available.

(63 patients) were removed as a primary surgical procedure, due to the extensive nature of the injuries. Secondary enucleation was required in 149 instances, 109 eyes being removed on account of severe structural damage, persistent intraocular inflammation, and risk of sympathetic ophthalmia. Some 61 eyes were enucleated within 14 days of injury, and the remainder at intervals up to several years post trauma. There were 2 cases of sympathetic ophthalmia, 1 of which was confirmed histologically. The other patient who developed sympathetic ophthalmia did not have surgical repair of the injuries because of poor general health. Enucleation was required most frequently following injuries sustained in road traffic accidents and civil disturbances, which were responsible for 27.8% and 23.9% respectively of all enucleations in the present series. A final visual acuity of 6/12 or better following blunt ocular trauma was obtained by 77.3% of patients in whom the final visual outcome was known, and 2.1% of patients in this category required enucleations. After perforating injury 45.5% of patients regained a visual acuity of 6/12 or better, but enucleation was required in 23.6% of cases. Intraocular and intraorbital foreign body injuries resulted in a visual acuity of 6/12 or better in 44.5% of patients, enucleation being required in 21.5%.

Discussion

Eye injuries were responsible for 8.7% of all ocular admissions to the Eye and Ear Clinic, Royal Victoria Hospital, Belfast, during the period 1967 to 1976. More than half (51.2%) of the patients were under 21 years of age and more than three-quarters (77.4%) were under 36 years of age. The high incidence of injury in males is illustrated by the male:female ratio of 5.25:1 compared with a

ratio for the population of Northern Ireland of 0.98:1. Approximately two-fifths (41.2%) of those patients for whom the final visual acuity was known regained 6/6 vision. However, the remaining three-fifths of patients for whom the final visual acuity was known suffered permanent diminution of vision. The high enucleation rate in this series (12.3%) reflects the severe ocular damage that often follows road traffic accidents and certain injuries associated with civil disturbances. This underlines the need for preventative measures.

Nearly one-third (32.5%) of the adult eye injuries were the result of road traffic accidents. These injuries showed a significant increase in the second quinquennium of this survey and were particularly serious, accounting for nearly one-half of the bilateral injuries and one-quarter of all enucleations. The typical ocular damage following road traffic accidents, a perforating eye injury associated with facial lacerations, is generally sustained by the front seat passenger who does not wear a seat belt.²⁶ Müller-Jensen and Allmaras²⁶ discussed 133 patients who sustained injuries in road traffic accidents and found that in 34% of this series there was a horizontal injury involving both eyes and the bridge of the nose. They and others^{27, 28} emphasised the importance of safety belts and laminated glass windscreens in preventing eye injuries. Mackay²⁹ found that approximately 70% of serious eye injuries in road traffic accidents were attributable to splintering of toughened glass windscreens, while those countries using laminated glass windscreens reported almost no eye injuries. The present publicity campaign aimed at increasing the use of seat belts is to be encouraged and compulsory fitting of laminated windscreens to all vehicles is strongly recommended.

In 1923 Garrow¹ reported that occupational injuries accounted for 70.7% of all eye injuries in his series. These figures are similar to earlier reports and are consistent with the industrial and social conditions of the time, including long working hours, child labour, and negligible safety precautions. Today industrial eye injuries occur less frequently than at the beginning of this century. They represent 15.4% of injuries in the present survey and show little or no decline during the 10-year period studied. Further enforcement of safety precautions in industry is indicated, in particular the use of shatter-proof glasses and visors which should be freely available. Their use should be encouraged by health education programmes arranged in collaboration with the trade unions. A further consideration might be to limit compensation paid for disability resulting from an ocular injury which could have been prevented if

appropriate protective measures had been undertaken.

Adult sports accounted for 4.8% of ocular injuries in the present study. Football (28%) and squash (17.1%) are the sports commonly implicated. Localised ocular injury is particularly frequent in squash, unlike football, in which eye injury is less common than injury to other parts of the body. In many sports, particularly squash and badminton, protective goggles could prevent ocular damage. These safety aids should be widely publicised on television and radio and their use encouraged in schools. Also, they should be readily available in sports shops, sports clubs, and recreational centres. The importance of such aids while playing squash and badminton has been emphasised by Ingram and Lewkonja,³⁰ North,³¹ and Chandran.³² Boxing, one of the classic causes of traumatic retinal detachment, is now better controlled and does not appear to be a common cause of eye injury, although lacerations to the orbital region occur in 2% of boxing matches.³³

Agricultural eye injuries were responsible for only 4% of the total injuries in this survey. This seems a low figure for a hospital in a community with a large rural population. Blake³⁴ reviewed injuries among agricultural workers and found that vegetable substances, particularly twigs and branches, caused most eye injuries. Injuries involving machinery and chemicals were less common and corresponded with figures published by Smith³⁵ in a similar survey in 1940.

It would have been anticipated that increased mechanisation of farm work would have led to a higher incidence of eye injury in recent years, although such an expectation is probably offset by a corresponding reduction in the number of workers employed in the agricultural industry. Since a large proportion of agricultural injuries in the present survey also were caused by vegetable substances, preventive measures should include protective goggles, and farm workers should be made more aware of their high risk with regard to this type of injury.

Eye injuries in the home encompass a wide variety of different types of accident and accounted for 6.8% of ocular injuries in this survey. These accidents predominate at either end of the age scale: 15.9% of injuries in the 0-5 year age group and 41.3% in the 66+ year age group. Accidents occurring to children at sport or during play were the most common cause of eye injuries in the present survey and were responsible for 33.8% of all known causes of ocular injury. Other types of injury in children were less common, comprising some 17.9% of childhood injuries. The general public should be made aware of the vulnerability of children to

certain types of injuries, e.g. catapults, darts, pencils, and sharply pointed instruments. Radio and television features and posters distributed to schools, clinics and health centres could be used to publicise the risk of such injuries. Health visitors also could contribute by offering mothers safety advice during routine consultations and visitations. Children should be encouraged to wear protective goggles during certain sports and while playing squash in particular.

We are grateful to the Eastern Area Health and Social Services Board for providing a research grant from the endowment fund of the Royal Victoria Hospital to facilitate this project.

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Desferrioxamine in ocular siderosis: a long-term electrophysiological evaluation

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SUMMARY Fourteen rabbits received an intravitreal iron foreign body and were treated with desferrioxamine. Their electroretinographic (ERG) values were recorded and compared with those of an untreated group. With desferrioxamine treatment a delay of the siderotic damage and preservation of better ERG potentials is observed.

The role of desferrioxamine (desferoxamine, deferoxamine) in systemic siderosis has been well documented.^{1–3} In ocular siderosis, although the drug had temporary acclaim, its value was found to be uncertain and controversial.^{4,5} The primary objective of this study was to investigate the electroretinographic changes in experimental ocular siderosis treated with desferrioxamine subconjunctivally. In our previous work we have shown that the earliest signs of siderosis are detected by electroretinography (ERG), long before histological evidence of iron in the retina is found.⁶ This prompted us to focus on the ERG changes in this experiment and to compare them with our data in untreated siderosis.⁶

Methods and material

Fourteen albino rabbits weighing between 2.8 and 3.5 kg were used in this experiment. For ERG recording the animal was sedated with an intramuscular injection of 25 mg chlorpromazine hydrochloride (Thorazine), installed in a restraining box, and placed in a shielded Faraday cage. The eyes were dilated with atropine sulphate 1% and tropicamide (Mydracyl). The cornea was anaesthetised with proparacaine hydrochloride 1/2% (Ophthaine). The ERG was recorded by means of a bipolar child-size eye contact electrode (Burian-Allen type). A drop of 0.5% hydroxymethylcellulose (Lyteers) was applied to the surface of the contact electrode. These conditions allowed for smooth electroretinographic recording, eliminating the need for general anaesthesia.

The ERG recording apparatus consisted of the

standard equipment for clinical electroretinography. ERGs were recorded binocularly by simultaneous stimulation with a Grass PS 22 photostimulator. The responses were fed into a differential amplifier and displayed on a Tektronix 5103 N storage oscilloscope. Polaroid pictures of the tracings gave us a permanent record.

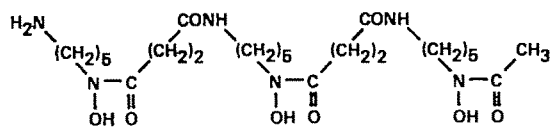
The ERG recording sequence was previously described in detail and has proved to give consistent and reproducible ERG recordings.⁶ In summary, in each recording session we used 3 different light stimuli. A photopic ERG was performed with white light intensity 8 (W8p); after 15 minutes of dark adaptation a scotopic ERG was obtained with white light intensity 1, attenuated by a neutral density filter of 1.0 log unit (W1ND) and white light intensity 8 (W8s).

In all experiments one eye was used as the experimental eye whereas the fellow eye was kept as the control, so that the A and B waves of the experimental eye could be expressed as a percentage of the intact fellow eye.

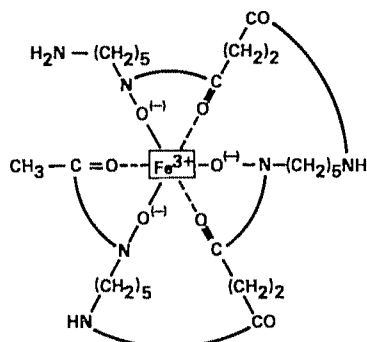
Implantation technique. A piece of pure iron wire, 0.25 mm in diameter, 3 mm in length, and 1.0 mg in weight was placed in a lumbar puncture needle gauge 22. The eye was entered through the pars plana. The iron fragment was then released in the vitreous under direct visualisation by advancing the stylet of the needle.

Desferrioxamine treatment. Desferrioxamine is a well known and potent iron chelator.⁷ It is a straight chain molecule which in the presence of a ferric iron ion (Fe^{+++}) wraps itself round it to form a complex known as feroxamine (Fig. 1).

Since previous experiments have shown that intravitreal desferrioxamine is very toxic, the sub-



Desferrioxamine



Feroxamine

Fig. 1 Desferrioxamine is composed of 1 molecule of acetic acid, 2 molecules of succinic acid, and 3 molecules of 1-amino-5-hydroxylaminopentane in a chain form, which can form the ferric chelate (=feroxamine).

conjunctival injection route was chosen.⁸ After topical anaesthesia with proparacaine drops desferrioxamine was injected through a gauge 26 needle. An initial dosage of 100 mg was given immediately after implantation of the foreign body. Subsequently 50 mg was given every other day for 2 weeks and thereafter 100 mg every other day for 3 more weeks. Since localised conjunctival oedema and irritation occurred after the injection, alternating quadrants of the eyeball were used. The ERG was recorded on the days no injection was given.

Results

Fig. 2 represents the ERG changes of ocular siderosis treated with desferrioxamine. The foreign body was implanted at time zero when the ERG of the experimental eye was the same as the one in the control eye. A decrease of 45% in the A wave and 25% in the B wave was observed on the second day. However, both A and B waves tend to become normal at the end of the first week. During the subsequent week a slow deterioration in the ERG potentials was observed. Thereafter a stabilisation of the A and B waves was seen up to 18 weeks after the foreign body had been implanted. At that time the A wave was 76% of the normal fellow eye and the B wave 81%.

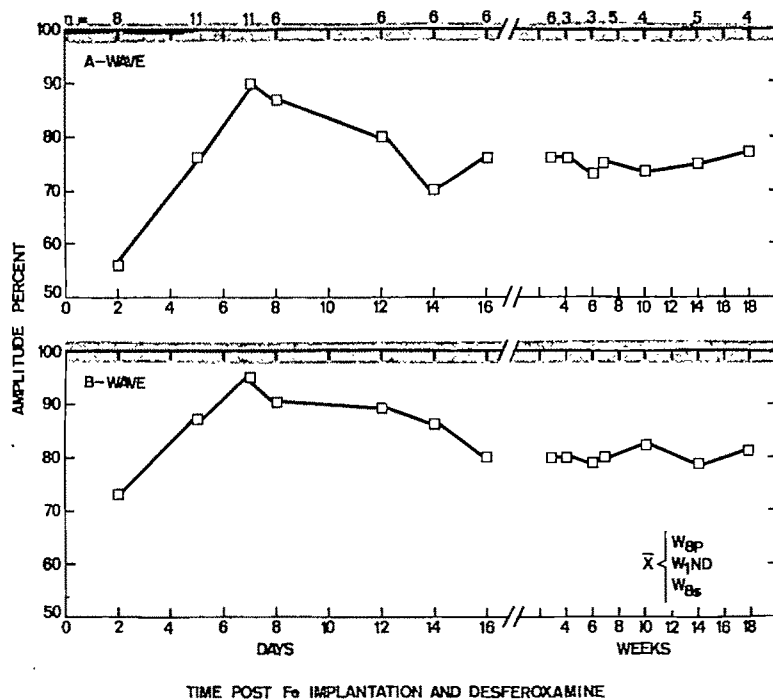
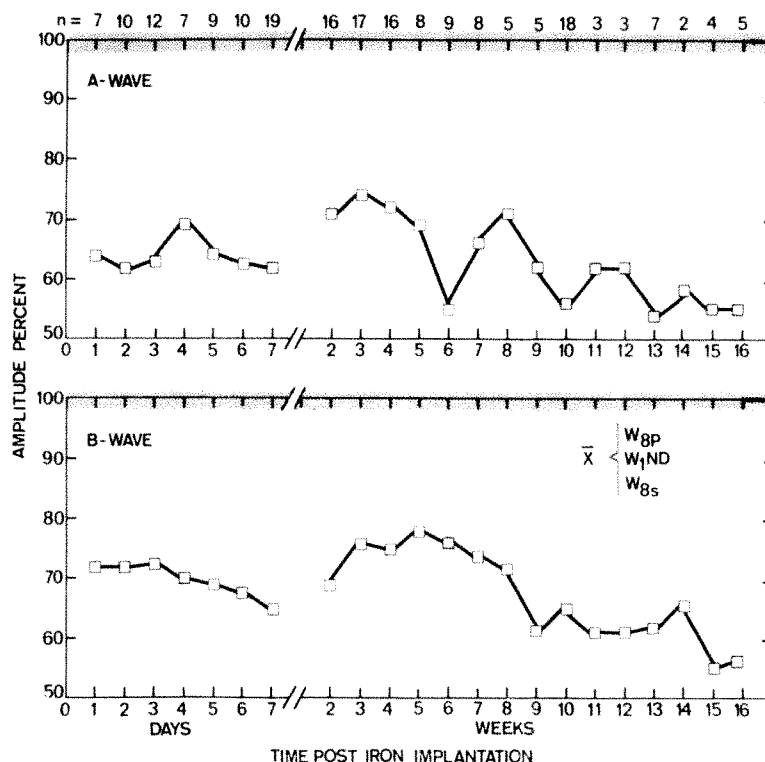


Fig. 2 A and B wave amplitude of iron implanted eyes, treated with desferrioxamine, as percentages of the intact fellow eyes. Each value represents the mean ERG under 3 different testing conditions of *n* rabbits tested at the given time.

Fig. 3 A and B wave amplitude of iron-implanted eyes as percentages of the intact fellow eyes. Each value represents the mean ERG under 3 different testing conditions of *n* rabbits recorded at the given time.



Discussion

To evaluate the effect of desferrioxamine treatment it is necessary to compare the data with those obtained in the absence of desferrioxamine. In addition the trauma caused by implantation of an intravitreal foreign body alters the ERG. Our previous work has shown that penetration into the vitreous cavity causes a temporary decrease of both A and B waves occurring at the second day after the trauma, with return to normal within 1 week.⁶ Hence we know that the drop in the ERG which we observed on the second day in this desferrioxamine study is due to the trauma per se.

Fig. 3 represents a summary of our previous studies done on 19 animals which received an identical iron foreign body without desferrioxamine treatment and were followed over a similar period of time. At the end of the first week the ERG values were down to approximately 63% of the normal fellow eye, and at the end of the 16th week they were down to 55% of the fellow eye.

The group treated with desferrioxamine showed a recovery to almost normal ERG values at the end of the first week. Thereafter a deterioration of A wave and B wave occurred, but in contrast to the untreated group the potentials stabilised at approxi-

mately 20% of the normal fellow eye by the end of the second week. These values remained unchanged up to 18 weeks after foreign body implantation, although the desferrioxamine had been discontinued after 5 weeks.

Both the recovery to almost normal values after the first week and the stabilisation later on with higher ERG potentials, despite the continued presence of an iron foreign body, are something we have never seen in animals not treated with desferrioxamine. One could postulate several hypotheses for this phenomenon, but we prefer to investigate further the effect of desferrioxamine in ocular siderosis and its potential usefulness in man before drawing any premature conclusions.

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Traumatic aniridia and aphakia with scleral buckling: a case report

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SUMMARY A case is reported of a young man in whom blunt injury caused a horizontal corneal tear superiorly. Aniridia, aphakia, cyclodialysis with angle recession, minimal hyphaema, vitreous haemorrhage, choroidal rupture and striae, and scleral buckling resulted. Vision improved to 6/12+.

Aniridia from blunt or perforating injuries usually occurs in association with severe damage to the eye.¹ Aniridia with aphakia resulting from such injuries is rare. To find cyclodialysis, angle recession, choroidal ruptures and striae, and scleral buckling associated with aniridia and aphakia with an intact vitreous face and minimal hyphaema must be unique. This case is reported because of these rare findings. Return of visual function in this case is also remarkable.

Malec² reported a case of aniridia and aphakia. Romem and Singer³ and Trobe and Keeney⁴ reported cases of traumatic aniridia with subsequent return to good visual function. Aviel and Avisar,⁵ Argento and Sampaulesi,⁶ and Bartkowska-orlowska and Orlowski⁷ reported cases of traumatic cyclodialysis and angle recession. Earlier reports of aniridia and aphakia were summarised by Duke-Elder and Macfaul.¹

Case report

A 30-year-old male, a bank attendant, was seen in the emergency outpatient clinic of the Guinness Ophthalmic Unit, Ahmadu Bello University Hospital, on the evening of 3 November 1978. About 2 hours previously he had sustained a blow with a clenched fist in his right eye. He then attended a private clinic, where the eye was cleaned and all 'leaking material' removed.

His visual acuity in the right eye was hand movements and in the left eye 6/6. There were no marks of violence nor any contusion or abrasion around the right eye. The conjunctiva was slightly congested. The cornea was clear, but there was a horizontal serrated wound superiorly from 10.30 to 2.00

o'clock position, resembling a too corneal, small incision for a cataract extraction. The anterior chamber was formed but rather shallow. A small hyphaema of about 2 mm was present. No iris was visible. The ciliary processes were clearly seen all round except inferiorly because of the hyphaema. The lens was absent. The vitreous face was intact and showed a streak of blood. The fundus was hazy, and details could not be made out. Slit-lamp examination confirmed these findings. A search was made in vain for the iris and the lens in the anterior chamber and under the conjunctiva.

The corneal wound was sutured under general anaesthesia. Again a search was made without avail to see if the iris and/or lens could be located under the conjunctiva or in the anterior chamber. The vitreous chamber was full of blood. Gonioscopically the angle appeared surprisingly clear except for a few small dots of blood and the hyphaema spread out in the inferior quadrant. The line of attachment of iris from where it was torn off could be made out. The eye was hypotonic, and so air was injected to bring up the intraocular pressure to optimum. Subconjunctival depot methyl prednisolone 20 mg and gentamicin 20 mg were given. Atropine drops and antibiotic eye ointment were applied and the eye was bandaged.

Postoperatively the patient was on systemic antibiotics for 7 days. Systemic corticosteroids were given from the first postoperative day in a short course on a gradually reducing regimen and were discontinued at the end of 2 weeks. On the first postoperative day the hyphaema had increased to about 3 mm, which cleared gradually. On the 9th day the intraocular pressure was raised (25 mmHg appplanation) and he was given acetazolamide 250 mg twice a day for 4 days followed by once a day for another 4 days, when the tension was found to have

returned to normal. Otherwise the postoperative period was uneventful and he was discharged on the 13th day to attend the outpatient clinic once a week.

When the hyphaema was absorbed an area of cyclodialysis between 5 and 8 o'clock position was detected. At the end of 3 weeks the vitreous was clearing up, and by the fourth week the fundus could be seen by the indirect ophthalmoscope. The disc and macula were normal. A linear raised ridge was found running in the lower half, anterior to the equator and parallel to it, almost like the appearance of an encircling band in retinal detachment surgery, in continuation of an area of choroidal rupture from 9.30 to 8 o'clock and ending in choroidal striae superonasally. In the periphery between 9 and 8.30 o'clock 3 blood dots were noted. No iris or lens could be located in the fundus.

Gonioscopy at this time did not reveal the iris either. The iris was torn cleanly and totally from all around. The angle was open. The inferior quadrant showed pigmentation on the trabeculum and the angle recessed in the area of cyclodialysis. The applanation pressure was 10 mmHg in the right eye and 12 mmHg in the left eye.

The following were the findings in the right eye: superior horizontal serrated corneal tear; aniridia; aphakia; small hyphaema; vitreous haemorrhage; cyclodialysis and angle recession; choroidal rupture and choroidal tear; scleral buckling.

At 2 months the eye condition remained essentially the same. The anterior segment did not show any further changes. The traumatic scleral buckling remained the same. The choroidal tears had become whitish, exposing the sclera and with pigment round them. The choroidal striae had also progressed to a similar pattern, and all these have a concentric appearance parallel with the equator, which is almost complete with only small discontinuity in between.

The right eye has remained quiet for the last 13 months. The visual acuity was counting fingers at 1 m, which improved to RE +7.50 sphere +2.75 cylinder 155°=6/12+. The intraocular pressure was 15 mmHg. The vitreous face remained intact. Gonioscopy did not show any changes except that the angle recession was seen to be minimal. No scleral buckling could be made out in the fundus now. The atrophic areas of choroidal damage were the only signs of the injury in the fundus at this time. The left eye was normal, with a visual acuity of 6/5.

Discussion

This case is interesting in many ways. After a heavy blow with a clenched fist the eye showed very little

reaction (minimal conjunctival redness, an almost clear cornea even with a rupture superiorly, a formed though shallow anterior chamber, and minimal hyphaema). A superior horizontal corneal tear is also surprising, though the cornea must have torn at the site of maximum impact.⁸ Almost invariably a total hyphaema accompanies every case of traumatic aniridia.¹ In this case, however, the hyphaema was slight. Except for the limited cyclodialysis there were no changes in the angle of the anterior chamber, which might explain this minimal hyphaema. Aniridia and aphakia occurred simultaneously, which is extremely rare, and it is more surprising because the lens had been extruded without disturbing the vitreous face in a young person.

Forces generated inside the globe at the moment of impact detached the iris completely, the returning wave of pressure from the posterior scleral wall forcing the vitreous against the lens and totally dislocating it. Both lens and iris were carried through the torn cornea, which 'leaking material' had been cleaned at the first place of attendance and so was lost to observation.¹ The choroidal rupture may be explained by mechanical factors, the globe being pushed against the bony orbit.

The scleral buckling observed in this eye has not been reported previously but can be explained by the same mechanical factor of the globe being forcibly pushed against the hard bony orbit. That this buckling was prominent in the inferior half is because greater force was exerted there by the fist, the inferior and lateral aspects of the orbit not being obstructed by the superior orbital rim and the nose. This scleral buckling smoothed out and the sclera regained its normal contour after about 9 months, which is also remarkable.

The transient rise of intraocular pressure could be due to traumatic inflammation in the trabecular area. The vitreous haemorrhage cleared rather rapidly, perhaps because of the early institution of corticosteroid therapy. The absence of any damage to the posterior pole of the retina, including the macula, helped the return of good vision.

Recovery after severe ocular trauma and regaining useful to excellent vision is increasing in frequency after the more recent practice of detailed evaluation of the injury^{4,7} and meticulous surgical management of these cases.⁸⁻¹³ Perhaps perfect coaptation of the various wound edges, thus restoring the normal anatomy of the eyeball, and reformation of the anterior chamber with air or balanced salt solution to restore normal intraocular pressure, are the 2 most important aspects in the management of severe ocular trauma after surgical cleanliness and combating infection.

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The congenital warfarin syndrome: a case report

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SUMMARY A case is reported of a baby born with congenital abnormalities due to maternal ingestion of warfarin during pregnancy. Warfarin is known to be teratogenic, producing characteristic abnormalities, namely, a hypoplastic nose, stippled epiphyses, and skeletal abnormalities. A variety of ocular abnormalities have been reported. Ophthalmologists should seek a history of maternal warfarin ingestion when seeing a baby with congenital ocular abnormalities. They should also be aware of the possible teratogenic effects when considering warfarin therapy for a woman of childbearing age.

It has been known for many years that oral anti-coagulants in pregnancy cause increased fetal loss and neonatal bleeding,^{1,2} but it is only recently that they have been implicated as a cause of congenital abnormalities. In 1966 Disaia³ reported the pregnancy of a woman with a prosthetic heart valve who was taking warfarin until the 36th week. The baby was born with various abnormalities including a hypoplastic nose and bilateral optic atrophy and was later shown to be mentally retarded. A causal relationship between vitamin K antagonists given in early pregnancy and characteristic fetal abnormalities was proposed by Kerber,⁴ and subsequently more cases were reported.⁵⁻⁷ Shaul and Hall⁸ reviewed the literature and reported on 14 abnormal children born to women who had all taken oral anticoagulants in early pregnancy. All 14 infants had a hypoplastic nose; 13 had bony abnormalities, the most characteristic being stippled epiphyses (chondrodysplasia punctata); 5 had ocular abnormalities.

Case report

A 24-year-old school teacher reported her first pregnancy at 12 weeks gestation in July 1977. She had first been prescribed warfarin in 1972 when she developed a pulmonary embolus while taking the oral contraceptive pill. After 6 months the anti-coagulant therapy had been discontinued, but she then developed a deep vein thrombosis in one calf and long-term anticoagulation with warfarin had been restarted. She continued to take warfarin until



Fig. 1 Baby's face, showing nasal abnormality due to mother's ingestion of warfarin.

December 1977 (at approximately 35 weeks gestation), when treatment was changed to subcutaneous heparin.

Spontaneous labour occurred at 39 weeks gestation, and a live male infant weighing 3000 g was delivered by forceps because of delay in the second stage. The baby was well at birth, with Apgar scores of 5 at 1 minute and 9 at 5 minutes.

Examination showed a term infant with a hypoplastic nose due to failure of development of the nasal septum (Fig. 1). No other abnormality was

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detected on routine clinical examination. X-rays of pelvis and femora showed stippling in the greater trochanters and left pubis and also abnormal vertebral bodies at S4/5.

In the first few days of life the baby had several dusky spells associated with difficulty in breathing, due to the tendency of the soft nasal structures to prolapse on inspiration. He gradually learnt mouth breathing and fed with difficulty from a bottle.

At 1 week of age he developed a sticky left eye, which was treated with chloramphenicol drops and ointment. Eye swab revealed a heavy growth of *Streptococcus viridans*. The epiphora persisted, and distention of the lacrimal sac was noted. Examination showed both eyes to be healthy. Each lens was clear and the optic discs were normal. He was discharged from hospital at 10 days of age on drops of chloramphenicol, and when seen again at 6 weeks of age the eyes were clean and the lacrimal sac no longer distended.

Discussion

Ever since their introduction oral anticoagulants have been used to treat thromboembolic complications of pregnancy, which usually occur in the second and third trimesters.⁹ However, there are now women who may be on oral anticoagulants at the time of conception and in the first trimester. These include the increasing number of young women with cardiac defects who have undergone valve replacements, and those women who have suffered a deep vein thrombosis or pulmonary embolus precipitated by an oral contraceptive.

In the case presented the mother was taking warfarin at the time of conception and in the first and second trimesters of pregnancy. The distended lacrimal sac (mucocoele) presumably stemmed from obstruction of the nasolacrimal duct associated with malformation of the nose. Such a mucocoele has not been previously reported, but the case described by Becker *et al.*¹⁰ had 'ectopic nasal lacrimal duct orifices'. The mucocoele resolved on conservative measures and probing was not necessary. This baby's eyes were healthy, but in the most comprehensive review of cases so far published* 5 of the 14 infants had ophthalmic abnormalities. These were optic atrophy (2), microphthalmia (1), lens opacity (1), and 'large prominent eyes' (1).

The combination of a hypoplastic nose, stippling of the epiphyses, and various skeletal and ocular abnormalities is found in Conradi's syndrome. This syndrome is a hereditary disorder occurring either as an autosomal recessive (rhizomelic) or an autosomal dominant (Conradi-Hunermann) form. It has been suggested that exposure of the fetus to a

vitamin K antagonist in early pregnancy may result in a similar phenotype to the dominant form of the disorder.^{11,12}

Warfarin is a relatively small molecule (molecular weight about 1000) and can cross the placental barrier. The way in which the drug may cause fetal abnormalities is unclear, but the production of microhaemorrhages in developing cartilage or a direct teratogenic effect have been postulated.⁸ An alternative anticoagulant, heparin, does not reach the fetus because it is a large molecule (molecular weight about 20,000) and it is highly charged. In contrast to warfarin it cannot be taken orally but must be given parenterally.

It is recommended that heparin is given instead of warfarin in the latter part of the third trimester and near the time of delivery in order to reduce the incidence of stillbirths and neonatal bleeding. However, in view of the association between the ingestion of warfarin in early pregnancy and fetal abnormalities it has become the practice in this centre to use subcutaneous heparin as soon as pregnancy is reported. It has more recently been suggested that fetal abnormalities, in particular ophthalmic abnormalities and mental retardation, follow the use of warfarin in the second trimester,^{11,12} and therefore the use of heparin alone throughout pregnancy is proposed.¹³ However, the incidence of fetal abnormalities due to warfarin in both the first and second trimesters is not known. More information is needed on which to base a rational policy of anticoagulation in pregnancy.

We suggest that the foregoing discussion is relevant to ophthalmologists on 2 counts. Firstly, women of childbearing age may present with ocular abnormalities, such as vascular occlusions, for which anticoagulants may be considered. The risks of pregnancy occurring during treatment must be discussed and contraceptive advice made available. Secondly, when a child with congenital ocular abnormalities presents, a history of the use of warfarin in pregnancy should be sought.

We are grateful to Mr I. E. Boyd and Dr C. J. Rolles, of Southampton General Hospital, for permission to publish details of this case.

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Book reviews

Topics in Neuro-Ophthalmology. Ed. H. STANLEY THOMPSON. Pp. 377. \$47.75. European Book Service: Netherlands. 1979.

The chapters in this book originated as contributions to a meeting in the University of Iowa in November 1977. As often happens, the delay in publication takes some of the gilt off what is essentially good gingerbread. The volume begins with some interesting papers on visual fields. There is a good chapter on the basic aspects of field testing and an appropriate warning that 'Goldmann perimetry is quite capable of producing falsely negative and falsely positive results'. Visual field examination is of course only one form of sensory examination. As in testing other modalities of sensation, the examiner must walk the narrow path between on the one hand paying too little attention to that aspect of sensory disturbance which is likely to be present, and on the other persuading the patient to agree to the sensory deficit the examiner expects to be present. It is also true that in sensory testing of any sort the intervention of too many mechanical devices, however elegant, between the patient and the examiner may lead more to error than to accuracy. The explanation of the difficulties of screen examination are certainly appropriate, but many would not agree with the limited role assigned to the use of the tangent screen in the exploration of central field defects.

The next series of chapters is devoted to pupillary abnormalities, including a useful chapter on the myotonic pupil, with an interesting account of patchy reductions of corneal sensitivity in association with myotonic pupils. Bell and Thompson found evidence of reduced pupillary response to light associated with tract lesions, while Corbett and his colleagues seem less certain of this. There are interesting papers on papilloedema and a discussion of the relevance of disturbances of axonal transport. The section on visual evoked responses and in particular new visual tests in multiple sclerosis are helpful reviews, as are the chapters on ocular movements. The last section on applications of CT scanning is of interest but has been rather overtaken by the rapid progress in this technique, with the development of coronal views, which in this volume receives only very brief mention.

C. J. EARL

Modern Problems In Ophthalmology: New Aspects of Vitreoretinopathology. Vol. 20. Eds. E. W. D. NORTON, C. GAILLOUD, N. DUCREY, M. GONVERS. Pp. 438. S.Fr.260. Karger: Basel, Switzerland. 1979.

This book gives an account of the proceedings of the eleventh meeting of the Gonin Club, held in Barcelona in October 1978. There are 87 papers discussing such diverse subjects as ciliochoroidal oedema, vitrectomy for intraocular foreign bodies, giant tears and diabetic eye disease, photocoagulation for inner and outer retinal disorders, functional results after retinal reattachment, explants, and muscle imbalance following surgery.

A somewhat cynical view of this expensive volume

might be that most, if not all, of the *valuable* presentations will be published elsewhere (probably within the time period taken for production of the book), while the remainder would doubtless fail to pass formal editorial scrutiny. Nevertheless, those contributions lacking in originality frequently provide a useful review of the subject, and the accounts of the post-session discussions, though disappointingly brief, help to put individual papers in perspective.

What is missing in any such volume, of course, is any overall structure or framework. A student might be forgiven for wondering, for example, why the Germans and Japanese attempt complicated, even computerised, measurement of subretinal fluid volume when most of us are happy to go along with Gonin and simply close the breaks. The book does, however, contain contributions from most of the leading authorities in retinal disease worldwide, and is a must for all with a special interest in the subject.

DAVID MCLEOD

Stereoscopic Vision. Proceedings of the Royal Society of London. Discussion organised by D. Whitteridge and P. G. H. Clarke. Pp. 518. £5.90. The Royal Society: London. 1979.

Some of the most distinguished workers in the field of visual physiology contributed to a discussion meeting at the Royal Society in March 1978, and this volume contains papers from the gathering. Although chiefly of interest to visual physiologists, some of the papers have implications that may attract those wishing to understand more deeply certain aspects of binocular vision in the clinical setting.

DAVID TAYLOR

Binocular Vision. By HOWARD SOLOMONS. Pp. 504. £18.75. Heinemann: London. 1978.

This book has been planned as a programmed text for students of optometry and ophthalmology. In particular the author hopes that it will provide a scientific framework to support orthoptists in their diagnostic and therapeutic work. Furthermore, since no prior knowledge of binocular vision is necessary, workers in other fields, such as psychologists, ergonomists, and visual scientists, may readily use it. The book is divided broadly into motor and sensory fusion, and the treatment within each section is complete and up to date. Wherever possible, figures from original papers or textbooks have been used, with full acknowledgements. Each chapter has a few well chosen references, mainly to important recent books, instead of a daunting list of papers which would otherwise be necessary in such a comprehensive volume.

Unfortunately the style is that of a lecture with the colloquial use of 'you'll see' and 'don't'. Nor must the reader be put off by occasional gross misrepresentation, such as occurs on page 5: 'Of course, neural impulses are electric, as they consist of the transmission of a change in the sign of the voltage along a nerve'. The repetitious style demanded by a programme text makes for tediousness in some sections. It is particularly important that the answers column should be correct, and

it is discouraging to find 'refractory' and 'dentrific' on page 98. Even worse is the consistent misspelling of Wiesel's name in the many references to his seminal work. Using figures from original papers has the danger that reduction in scale has made some illegible. It is harder to excuse the almost impenetrable fundus photograph on page 273.

It would be easy to give more examples of similar mistakes in details, and this would be to ignore the many good ideas and clear exposition of difficult subjects such as horopters, space perception, and stereopsis. It is easy to correct spelling and the quality of reproduction of figures. The inclusion of red and green anaglyphs with viewing spectacles for depth perception would be a great advantage.

It is to be hoped that these minor criticisms will be taken to heart for the next edition, since the general concept of the book is to be admired and it will undoubtedly deepen the understanding of all who read it.

PETER FELLIS

Fortschritte der Kiefer-und Gesichts-Chirurgie. Vol. 24. **Plastische Chirurgie im Mund-, Kiefer-und Gesichtsbereich.** By H. von Karl Schuchardt and Norbert Schwenzer. Pp. 151. DM190. George Thieme Verlag: Stuttgart. 1979.

This book is a collection of articles on plastic surgery of the face and head. The topics which may be of interest to an ophthalmologist include the treatment of some bony defects in the skull and periorbital region, blepharochalasis, port-wine stains, and dermabrasion. There are a good series of clinical photographs, but since the book is written in German and most of the articles do not relate to ophthalmology I doubt whether it will be of much value to readers of this journal.

J. R. O. COLLIN

Advances in Ophthalmology. Vol. 39. Eds. M. J. ROPER-HALL, H. SAUTTER, E. B. STREIFF. Pp. 273. S.Fr188. Karger: Basel, Switzerland.

This multiauthor, multilingual book contains 6 chapters on varying aspects of ophthalmology. Subjects include pathophysiology of the retinal circulation (French), mitotic properties of the pigment epithelium (German), and the P-32 test (German). The 3 papers in English are on retinoblastoma, ultrastructural changes in the iris after laser, and ocular manifestations of demyelinating disease. Much of this information is provided elsewhere in original papers, so that at £49 this would appear an expensive purchase.

M. D. SANDERS

Ocular and Adnexal Tumors. By FREDERICK A. JAKOBIEC. Pp. 929. Dutch Guilders 260. Kugler Medical Publications: Holland. 1978.

This very well produced large book brings together in 58 chapters contributions from 71 authors, all of whom are personally concerned as clinicians and pathologists in the diagnosis and treatment of patients with the misfortune to have some type of neoplastic disease involving the eye, the orbit, and its neighbouring tissues. This outstanding volume is dedicated to the memory of

the late Dr Algernon B. Reese, who personally contributed so much to this aspect of ophthalmology in his writings, in his personal care of patients, and in the teaching of those who had the privilege of attending or working in his department. It is edited by, and includes several contributions from, one of his disciples—Frederick A. Jakobiec, who is now director of the A. B. Reese Laboratory of Ophthalmic Pathology at the E. S. Harkness Eye Institute at the Columbia-Presbyterian Hospital, New York.

The text is very clearly printed and therefore a pleasure to read. There are over 800 illustrations, including well reproduced clinical photographs, histological photomicrographs, x-rays, ultrasound, and CT scans and tables; references to the literature follow each separate chapter. There is an author index and subject index.

All aspects of the pathology, natural history, clinical diagnosis, methods of investigation, treatment, and prognosis of ocular and adnexal tumours are considered in 5 sections. These deal successively with intraocular melanoma; nonmelanomatous intraocular tumours, including retinoblastoma and vascular lesions; diagnostic techniques, including isotope uptake tests, ultrasound and CT scanning, cytology, enzyme studies, and immunology; lid and conjunctival tumours; inflammations and tumours of the orbit. The text includes the first A. B. Reese memorial lecture by L. Zimmerman on the histogenesis of conjunctival melanoma, and this follows an outstanding clinicopathological study of this disease contributed by the editor and his colleagues and an account of its natural history by P. Henkind.

Many chapters include comments and discussion about the various methods of treatment that are available for ocular and orbital tumours. These include radical removal by enucleation, or exenteration of the orbit and the various techniques of localised surgical excision with preservation of lid, conjunctiva, and the eye; also methods which attempt to destroy the tumour in situ by diathermy, photocoagulation, cryotherapy, chemosurgery, and the various techniques of radiotherapy. There is some discussion of the advantages and disadvantages of observation without specific intervention unless there is unequivocal evidence of actual growth in certain tumours.

The major content of this book, however, concerns description of the detailed pathology of certain ocular tumours, including some relatively rare conditions. Each of these chapters individually is excellent but especially that concerned with the ultrastructural characteristics of ocular tumours, which itself occupies nearly 100 pages and is accompanied by excellent illustrations.

Without any doubt this beautifully produced volume, reflecting the work of many people, is an outstanding contribution to the literature of ophthalmology. To those particularly concerned in their clinical work with patients having some type of ocular tumour it will be a great source of information and help, and they certainly will wish to obtain the book for their own personal use. It certainly should be made available in the libraries of eye hospitals and also in those hospitals whose pathologists are called on to help in the diagnosis of ocular tumours.

P. A. MACFAUL

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Arachnoid hyperplasia in optic nerve glioma

SIR, In the September 1979 issue of the *BJO* Cooling and Wright¹ have attempted to account for the curious fact that in their experience only 1 of 20 patients with meningiomas of the optic nerve was a child, whereas from the combined case material in the Registry of Ophthalmic Pathology of the Armed Forces Institute of Pathology, and at the University of California, Karp *et al.*² reported that 7 of their 25 cases involved children who were 11 years old or younger, and 10 patients (40%) were younger than 20 years. Cooling and Wright offer as their explanation for this difference in experience the possibility that the pathological diagnoses in the paediatric cases of Karp *et al.* were incorrect. They base this suggestion on their own unfortunate experience in having had to operate on a child 3 times before the correct diagnosis of glioma was established.¹ Biopsies at the first 2 operations had led to a diagnosis of meningioma, but in fact it was subsequently shown that arachnoidal hyperplasia associated with a glioma had been mistaken for meningioma. The Editor of the *BJO* was stimulated to prepare an editorial on the subject which was carried in the same issue.³

That exuberant meningeal hyperplasia may be observed in association with gliomas of the optic nerve is a fact that has been well appreciated by ophthalmic pathologists for over half a century. Two of the authors of the original paper in question (Zimmerman and Spencer) have written on this subject⁴⁻⁷ and have for many years in their lectures cautioned about making this error in pathological diagnosis. Curiously, Cooling and Wright even cited some of these publications^{1,5} in support of their argument, including the fact that Hogan and Zimmerman⁴ pointed out that there is 'the possibility of diagnostic confusion between arachnoid (sic) hyperplasia accompanying a glioma, and orbital meningioma'.

To document further our concern about correct histopathological interpretation I would like to take this opportunity to comment on another strange case report that appeared in the *BJO* in 1977.⁸ The authors interpreted their tumour as a mixed meningioma and astrocytoma, though judging from their published illustrations I suspected they had misinterpreted arachnoidal hyperplasia for meningioma. At my request the senior author kindly permitted me and my colleagues to review a histological section of this tumour, which confirmed to our satisfaction that the 'meningioma' was in fact arachnoidal hyperplasia. We are therefore well aware of the possibility for such errors in histopathological interpretation, but they are not attributable to the pathologist's absence from the surgeon's side in the operating room.

The glib implication that in the series by Karp *et al.*² the pathological diagnoses must have been made by inexperienced pathologists so removed from the surgical scene that they couldn't possibly make the correct diagnosis cannot be allowed to stand without challenge.

Any pathologist who has had any experience in the differential diagnosis between arachnoidal hyperplasia and meningioma should recognise at a glance that the illustrations contained in the paper by Karp *et al.* (their Figs. 1 through 6)² cannot be accounted for by hyperplasia. It is customary among pathologists and clinicians of mature judgment to request an opportunity to review histopathological preparations before publishing such allegations as Cooling and Wright have done. Karp and his colleagues have never been asked to give Cooling or Wright an opportunity to study sections of the tumours from their paediatric cases. There was no correspondence relative to this problem between Cooling and Wright, on the one hand, and Karp *et al.* on the other.

In retrospect it is unfortunate that we did not include in our paper a section on differential diagnosis between meningeal hyperplasia and meningioma. This experience will serve as a stimulus for a more detailed future report on the subject, but for the present I would like to point out some basic differences that even surgeons who are not knowledgeable about ophthalmic pathology should be able to appreciate. (1) In arachnoidal hyperplasia the proliferation remains intradural, whereas in most meningiomas there is invasion through the dura into the surrounding orbital tissues, as was so clearly evident from Figs. 1 and 4 in the paper of Karp *et al.* (2) Orbital recurrences with or without intracranial involvement are common complications after operations on meningiomas of the optic nerve in children (one of the main points of the paper by Karp *et al.* ignored by Cooling and Wright), but this never (in our experience) occurs with meningeal hyperplasia. (3) Meningiomas are potentially lethal tumors, especially in children, whereas meningeal hyperplasia is not.

To document further and augment the validity of the data presented by Karp *et al.* I can, through the courtesy of Dr Melvin G. Alper,⁹ who restudied and updated the Registry case material last year in preparation for his Francis Heed Adler lecture on orbital meningiomas, give some additional follow-up information on the paediatric cases in Karp *et al.*'s series:

Case 2. This patient, who was 6 years old at the time of enucleation and whose massive meningioma was illustrated in Fig. 4, had further recurrences with intracranial involvement and died at age 31.

Case 3. This child, who was 6 years old at the time of initial surgery, was the only prepubertal child who was living without recurrence at the time of the initial report. However, she developed an orbital recurrence and died of a viral infection at age 13. Invasion of the eye was also observed postmortem.

Case 8. Five years after the initial excision of the meningioma this patient had an exenteration followed by a transcranial exploration because of a recurrence of the tumour.

The aggressiveness of these meningeal tumours in young patients clearly reflects the fact that they are truly neoplastic and not merely reactive processes as suggested by Cooling and Wright.

In summary, the clinical course and the typical histopathological features of the paediatric tumours reported

by Karp and coworkers establish beyond reasonable doubt that these were meningiomas, not gliomas with meningeal hyperplasia. While we have no explanation for the almost total absence of meningiomas in British children, I can report that since the publication of Karp *et al.* we have seen additional cases in the United States. Messrs Cooling and Wright must seek a better explanation for their different experience.

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defence.

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SIR, We were very interested to read Professor Zimmerman's comments about our paper. The purpose of our communication was to highlight the difficulties facing the pathologist receiving histopathological material without adequate clinical information. Our presumptive clinical diagnosis was an optic nerve glioma, when the child detailed in the case report was first seen. However, when the normal intracanalicular portion of the optic nerve with its surrounding abnormal tissue was examined by an experienced neuropathologist, the neurosurgeon failed to inform him that the main part of the tumour lay within the orbit. The pathologist incorrectly diagnosed a primary optic nerve meningioma.

We fully accept Professor Zimmerman's statement that all the patients reported by Karp and his associates¹ were meningiomas. His expertise in this and other fields is unquestioned, and we acknowledge that he has selected patients with tissue that he has diagnosed correctly as meningioma. We therefore withdraw our statement that some of his patients may have had arachnoid hyperplasia remote from an unsuspected glioma.

However, the reported incidence of primary optic nerve meningioma in childhood is very low in all recently reported series of this lesion²⁻⁴ except that of Professor Zimmerman and his colleagues. There are 2 possible explanations which may account for this discrepancy. (1) The 10 children they recorded all had a primary optic nerve meningioma. It is possible that the increased incidence may be due to selection. They reported 21 specimens out of a total of 81 dating back to 1927. (2) All patients had a meningioma but a proportion of these were secondary in origin, i.e., there was extension into the orbit from the middle or anterior cranial fossa. This is a distinct possibility for, no matter how expert the pathologist, he is dependent on the accuracy of clinical information supplied by surgeons in centres of differing excellence, often using the primitive diagnostic facilities in an earlier era. Therefore one cannot be absolutely sure of the origin of the meningiomatous tissue in order to correctly classify the meningioma as a primary optic nerve tumour.

The expertise of Professor Zimmerman and his associates is beyond question, but they have in many cases been dependent on clinical details sent them with the excised specimen. As an example of this, a recent report from the A.F.I.P.⁵ detailed their experience of optic nerve gliomas. The authors found that the incidence of associated neurofibromatosis was only 10%, one of the lowest reported in any series. Their explanation was that the low incidence was probably due to the inadequate clinical information provided by those referring the specimens to the A.F.I.P.

Our experience and that of others differs from that of Professor Zimmerman and his coworkers. During the past 5 years there has been 1 case of primary optic nerve meningioma occurring in a child in the combined clinical London experience of Moorfields Eye Hospital, the Hospital for Sick Children, Great Ormond Street (David Taylor, personal communication), and the National Hospital for Nervous Diseases (W. I. McDonald, personal communication). During the same period 12 primary optic nerve meningiomas were seen in adults.

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Obituary

Hugh Campbell Orr, MB, ChB, FRCP(Glas)

Hugh Campbell Orr, formerly consultant ophthalmic surgeon to Wolverhampton and Midland Counties Eye Infirmary, died on 30 April aged 81. He was born at Hamilton, and during the first world war enlisted in the Royal Artillery, serving 3 years in France. He graduated in medicine from Glasgow University in 1924 and shortly afterwards was appointed house surgeon to Wolverhampton Eye Infirmary. He had originally intended to take up neurology, but Ophthalmology claimed him and he never regretted his change in direction. He was appointed assistant surgeon in 1925 and, after qualifying FRFPS (Glasgow), honorary surgeon in 1934. His desire for progress frequently led him into dispute with the governing council of the hospital, but the force of his argument and his determination usually won the day. With the introduction of the National Health Service he became consultant surgeon, and after his retirement from the service in 1963 he continued in his private practice, school clinics, and general ophthalmic services work.

His professional career spanned years in which tremendous changes occurred in ophthalmology, with progressive refinement of surgical instruments and technique, and it says much for his ability that he always kept abreast of these developments, maintaining that surgeons could not mark time, only go forwards or backwards. His early interests were in industrial injuries and retinal colour photography, but in later years he became more interested in vascular and degenerative diseases of the retina and was a firm believer in the value of vasodilator drugs. Greatly troubled by the increasing number of patients referred with senile macular degeneration, against current thought he foresaw the possibility that it might eventually yield to treatment and merited thorough investigation. Although he did not have the facilities to do research into the condition himself, he encouraged others to do so and the renewed interest of recent years gave him considerable satisfaction.

During the postwar years he travelled much in Europe

and was held in high regard by many ophthalmologists whose clinics he visited. Apart from the strictly formal rounds on these occasions he valued as much the free discussions on ophthalmic matters and interchange of ideas during the social gatherings. He was never afraid to defend his often controversial views, but after a hard-fought disputation would often wryly quote from his favourite Omar Khayyam: 'Myself when young did eagerly frequent, Doctor Saint, and heard great argument About it and about; but evermore Came out by the same door as in I went'.

He had a reputation as a strict disciplinarian towards both his patients and his staff, but he took great pains to teach surgery to his juniors, and although they went in daily fear of his disapproval he and Mrs Orr were charming and generous hosts when they entertained successive house surgeons and registrars to an evening's relaxation at the theatre at Stratford-on-Avon. His work dominated his whole life, and practically his only leisure activity was reading, but in later years much time was devoted to his only daughter, disabled by chronic illness, whose death came only a few weeks before his own.

For many years he was the secretary of the Staffordshire Branch of the BMA. He was president of the Midland Ophthalmological Society in 1947-9 and in 1971 served as deputy master of the Oxford Congress, where he was a familiar figure.

The theme of Hugh Campbell Orr's life was to work and to serve. He served the local community well as an ophthalmologist and his name was a byword in Wolverhampton; and he worked until only 5 days before his death—truly a life-time of dedication to his calling.

B.R.K.

Notes

Courses at Institute

The following courses will be held at Institute of Ophthalmology: Revision course in eyelid and lacrimal surgery, 27-29 October 1980 (fee £50). Recent major advances in the management of ocular trauma, 26-28 November 1980 (fee £75). Indications and techniques in the ophthalmic management of retinovascular disease, 1-3 December 1980 (fee £75). Applications to the Dean's Office, Institute of Ophthalmology, 17-25 Cayton Street, London EC1V 9AT.

Laser workshop

A laser workshop for ophthalmic diseases will be held at the Singapore General Hospital on 26-28 September 1980. It is organised by the Academy of Medicine, Singapore, and the Australian College of Ophthalmologists. Details from Laser Workshop, 606-610 Singapore Polyclinic, Specialists' Centre, Orchard Road, Singapore 0923.

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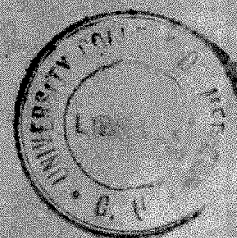
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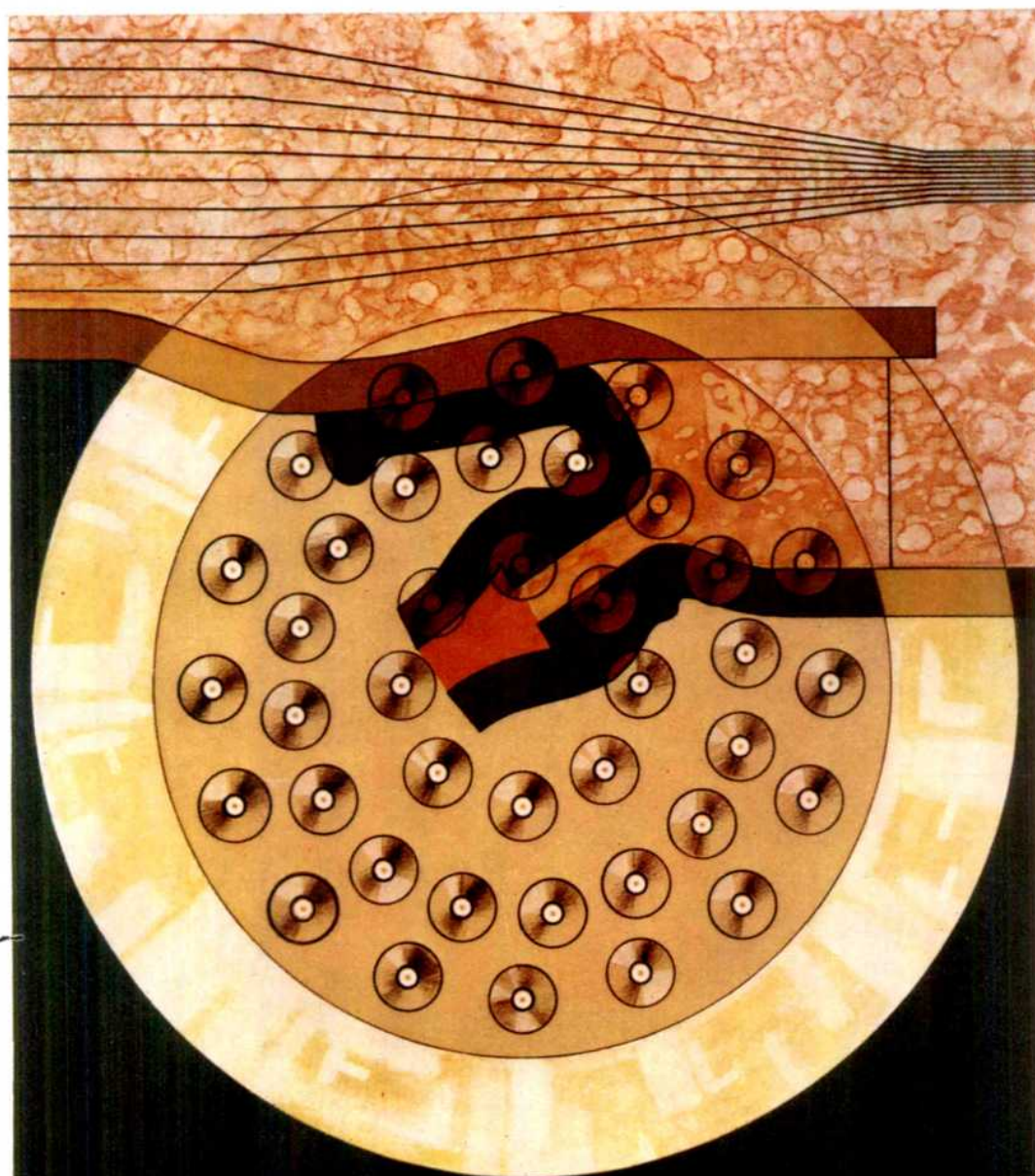
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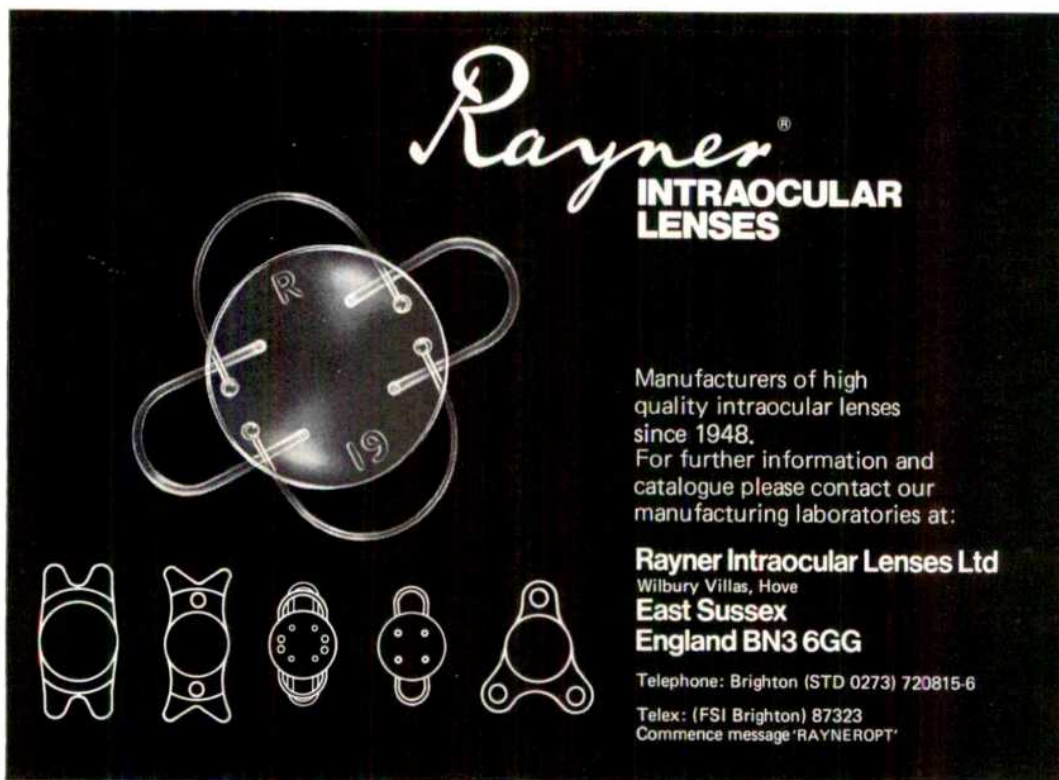
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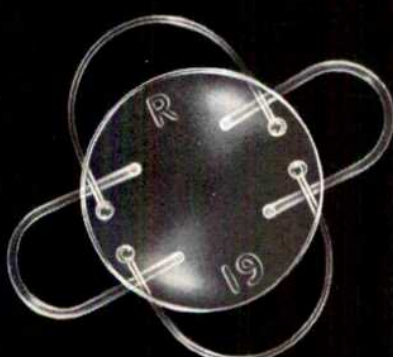
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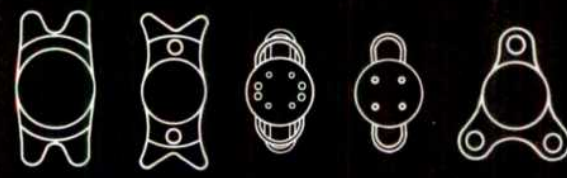
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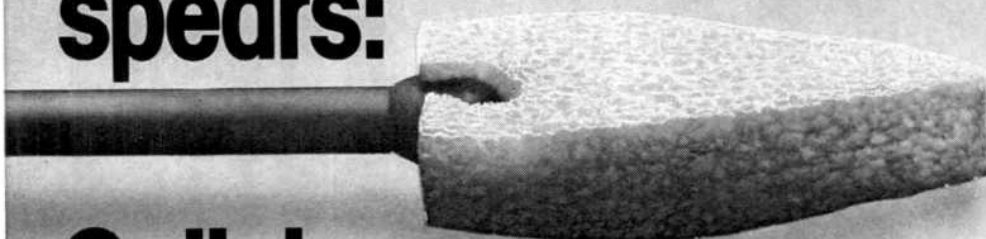
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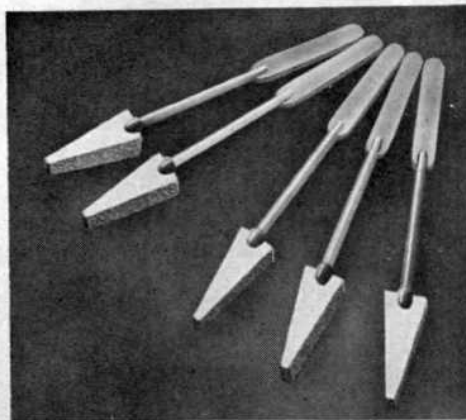


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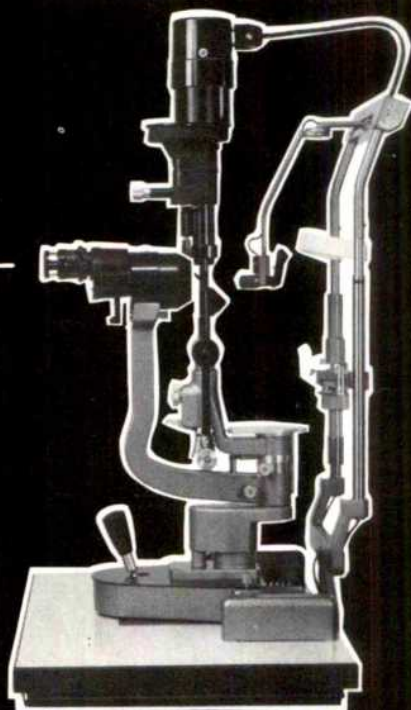
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Photography of the retinal nerve fibre layer: an optimised procedure

LARS FRISÉN

From the Department of Ophthalmology, University of Göteborg, Sweden

SUMMARY Normal and abnormal fundi were photographed at various magnifications in one and the same fundus camera, with and without 'red-free' filters and various types of black-and-white and colour films. Colour diapositive films were copied on various black-and-white negative films, with and without filters. The final negatives were evaluated under magnification with regard to resolution and contrast of detail in the nerve fibre layer. Complementary information was obtained by means of conventional resolution measurements at high and low contrast levels. The best overall results were obtained by copying colour slides obtained in unfiltered light on a new high-contrast black-and-white film (Kodak Technical Pan), with a Wratten No. 65 A filter. This simple technique produced negatives with a good definition of the nerve fibre layer, suitable as final records.

Photography of the peripapillary retinal nerve fibre layer has attracted considerable interest during recent years. In spite of the potential of this new diagnostic technique, its universal application has been lagging. This is mainly due to the difficulties of visualising the faintly opaque nerve fibre bundles in ordinary fundus photographs. Maximum use of this technique therefore demands special quality control. Several reports have dealt with the optical properties of fundus cameras,¹⁻⁴ focusing techniques,⁵⁻⁶ filters,⁷⁻¹¹ films and developers,^{2,12,13} and printing procedures.¹⁴ However, a unifying study aiming to find optimum combinations has not yet appeared. It is the aim of the present report to fill this gap.

The overwhelming number of possible combinations of camera types, filters, films, and processing techniques makes a full permutation of variables practically impossible. This study was therefore limited to one modern camera, a single source of films and film developers, and a small number of carefully selected filters. Furthermore, this study concentrated on the production of optimum results in black-and-white. Colour materials are not only much more expensive than black-and-white materials but they are also more difficult to manipulate technically. The improved visibility of the retinal nerve fibre layer in green ('red-free') light also favours black-and-white documentation.⁷⁻¹¹ Even

with these restrictions more than 3000 photographs had to be evaluated in this study.

Numerous normal and abnormal fundi were photographed at various magnifications in one and the same fundus camera, with and without green filters, with various types of films and film developers. Complementary information was obtained by means of conventional resolution measurements at high and low contrast levels. Colour diapositive films were copied on various black-and-white negative films, with and without green filters, with both photographic reproduction and contact copying. The final negatives were evaluated under high magnification with regard to resolution and contrast of detail in the nerve fibre layer. The best overall results were obtained by contact copying colour slides obtained in unfiltered light on a new high-contrast black-and-white film (Kodak Technical Pan), with green light. This simple technique produced negatives of very good definition of the nerve fibre layer, highly suitable as final records. The contrast was actually so high that direct printing on photographic paper led to image degradation. For good printing results unsharp masks proved to be valuable.

Materials and methods

The fundus camera used was an adapted Nikon Retinapan II. The original focusing screen was replaced by a full-format clear screen with a fine reticule pattern, and the original viewfinder was

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Table 1 *Films and developers; manufacturer's data*

Film name	Sensitivity ASA	Graininess ¹	Sharpness	Resolving power lines/mm at high/low contrast	Developers
Kodachrome 25	25	Extremely fine (9)	High	100/50	Kodak Laboratory
Kodachrome 64	64	Extremely fine (10)	High	100/50	Kodak Laboratory
Ektachrome 200	200	Very fine (13)	High	125/50	Kodak Laboratory
Panatomic-X	32	Extremely fine	Very high	200/80	Microdol
Technical Pan	100	Extremely fine (8)	Not stated	320/125	HC-110, D-19
Plus-X Pan	125	Extremely fine	Very high	125/50	Microdol, D-11
Tri-X Pan	400	Fine	Very high	100/50	Microdol

¹RMS granularity values given when available.

replaced with a Nikon DW-2 6X viewfinder, to facilitate precise focusing. For critical focusing at the lowest magnification ($1.7\times$, nominally), a $2\times$ Galilean telescope was superposed on the viewfinder.

The camera was used both with and without magnification attachments. Two attachments were available: the original conversion tube (giving $5\times$ magnification, nominally), and a Nikon TC-200 teleconverter (allowing nominal magnifications of $3.4\times$ and $10\times$).

Resolution measurements were carried out as has been described previously.⁸ In brief, low-contrast and high-contrast NBS resolution charts were placed 1.5 m in front of the camera objective on its optical axis. The charts were photographed at various magnifications on different types of films. The DW-2 viewfinder was then replaced with a small $30\times$ microscope, resting on the focusing screen. This served to ensure perfect focusing. Focus was adjusted for each new frame of film. After development the various films were evaluated at $40\times$ in a stereo microscope. Resolving powers were calculated in lines per millimetre.¹⁵

Films and developers were all produced by Eastman Kodak Company. Three colour diapositive films of different sensitivity were included, namely, Kodachrome 25 and 64, and Ektachrome 200. Appropriate light-balancing filters were used in the resolution study. The black-and-white films included Tri-X Pan, Plus-X Pan, Panatomic-X, and Technical Pan (SO-115). The manufacturer's rating of various film properties is given in Table 1 together with information on the various development procedures. The black-and-white films were developed immediately after exposure, while the colour films were developed by a Kodak laboratory within a few days of exposure.

Copying of colour films on to black-and-white films was done both photographically and as a

contact procedure. A Bowen's Illumitran served as the flashlight source for photographic copies. A Nikon F2 camera body combined with a clear focusing screen and a $30\times$ focusing microscope was used together with several different types of objectives. These will be further described below. The reproduction scale was usually 1:1.

Contact copies were produced in a simple apparatus with tungsten light (Fig. 1). A 2.5 mm diameter aperture admitted light through a clear glass copying

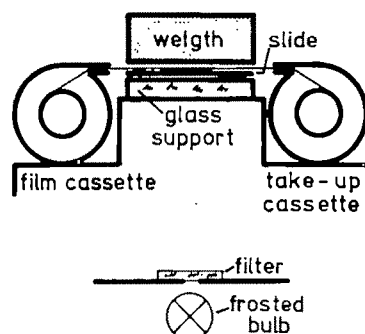


Fig. 1 *Scheme of apparatus used for contact-copying (not to scale). See text for details.*

stage, which was placed 0.3 m from the aperture. Various filters could be interposed in the light beam. The slide to be copied was placed on the glass support, with the emulsion side up. In total darkness a suitable length of copying film was drawn out from its cassette and placed on top of the slide (emulsion side down). Registration was obtained by means of small knobs engaging the film perforations. A small weight pressed the film and the slide against the glass stage during exposure. The exposed portion of the film was then lifted off the stage and

drawn into an empty cassette. The room light was then turned on, the slide changed, the light turned off, a new length of negative film drawn out, and so on.

Filters were used both in the fundus camera and during copying. They were selected to cover the most useful spectral range.⁷⁻¹¹ A green Wratten filter of 26.2% transmittance (No. 40) was sometimes used in the fundus camera. A denser filter was used during copying, either a Wratten No. 65A (transmittance 6.2%), or a medium bandwidth (spectral half-width 25 nm) interference filter. Dominant wavelengths for the gelatin filters were 513.4 nm and 497.3 nm respectively. Maximum transmission for the interference filter occurred at 480 nm.

Evaluation of image quality was made subjectively under 8–40 × magnification, attention being paid primarily to contrast, sharpness, and graininess.¹⁶ Except for the resolution measurement described above, most evaluations were carried out by ranking series of coded images. The code was not broken until 2 sequential rankings produced exactly the same results.

Results

Resolving powers were obtained for both high and low contrast levels for all films, at all magnification settings. The results are summarised in Fig. 2. The maximum number of resolved lines per millimetre was always considerably smaller than the resolving power indicated by the film manufacturer (cf. Table 1). Similar results have been reported for the Carl Zeiss fundus camera.² These results indicate that the fundus camera seriously limits the resolution that can be obtained in fundus photography. The maximum number of lines per millimetre was obtained at the lowest magnification: as magnification attachments were added, resolution in terms of lines per millimetre in the film image went down. This effect was counteracted by a larger number of resolved line groups at higher magnifications.

The 2 slower colour slide films produced the best results throughout. It was usually impossible to tell the 2 films apart. The more rapid colour diapositive film produced consistently poorer results (Fig. 2).

Among the black-and-white films there was a very striking difference between Technical Pan on the one hand, and Plux-X Pan, and Tri-X Pan on the other (the VTE Pan film recommended by Frisén² is no longer available). The former film produced pictures with considerably better resolution at both high and low contrast levels (Fig. 2). Technical Pan was developed in D-19 for 2 min at

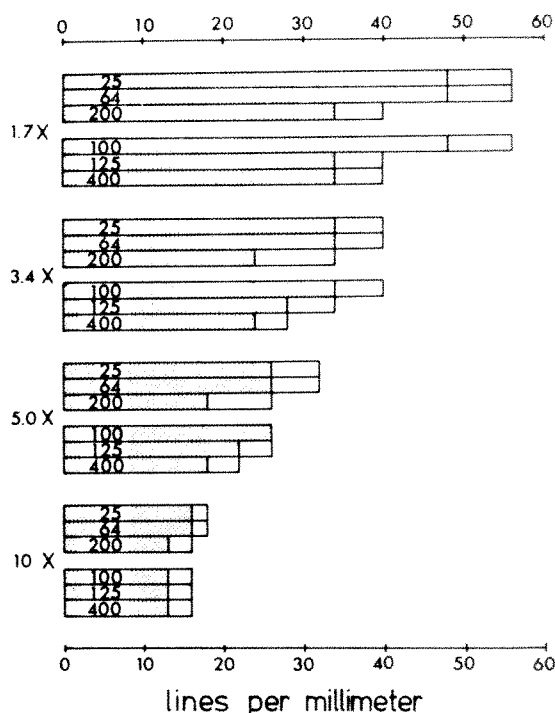


Fig. 2 Resolution obtained at high and low contrast levels with different films, with and without magnification attachments. The films are identified by their ASA values (cf. Table 1).

20°C, the other black-and-white films in Microdol 1+3 according to the manufacturer's recommendations.

The results described here apply only to on-axis imagery. Off-axis imagery is more difficult to assess in a way meaningful to fundus photography.²

Colour diapositive fundus photographs. The 2 slower colour slide films showed highly similar results. The images were subjectively judged to be sharper and more finely detailed than those produced by Ektachrome 200. Kodachrome 64 appeared to be the film of choice for regular fundus photography. The best compromise between field size, resolution, and depth of focus, was obtained at the 3.4 × magnification setting (Fig. 3A).

There was a more pronounced graininess in the slides obtained with filtered light. The green filtering did enhance the contrast of the nerve fibre layer to a moderate degree, but the simultaneous increase in image graininess tended to offset this advantage. It is possible that 'red-free' pictures of higher quality could have been obtained had only the fundus camera flash aggregate possessed a higher output. Within the limits of the available equipment,

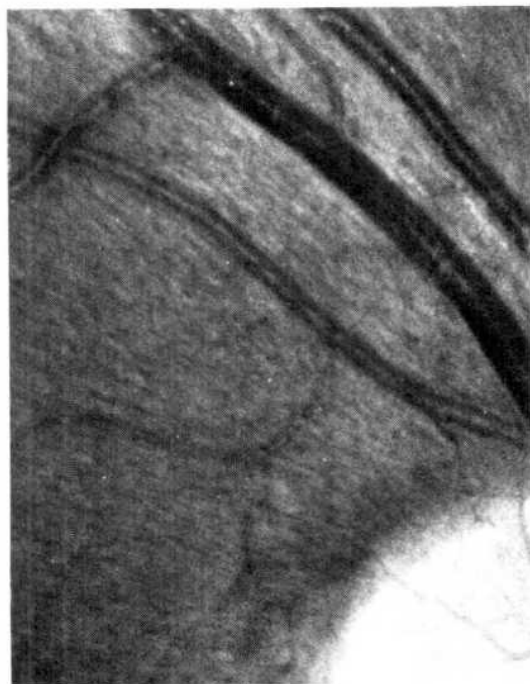


3A

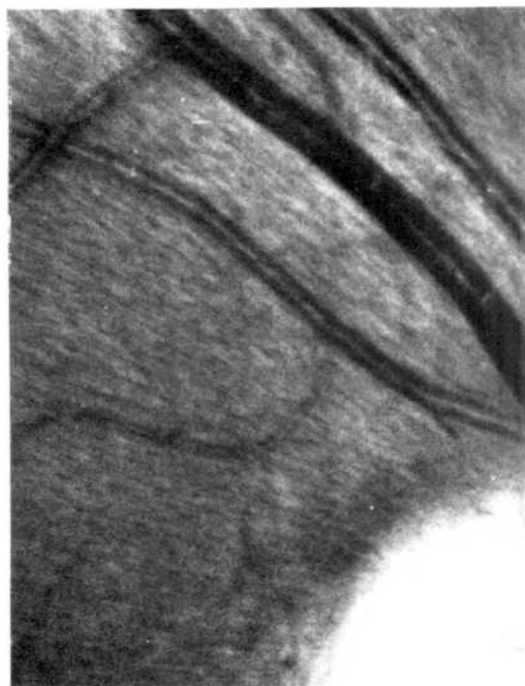


3B

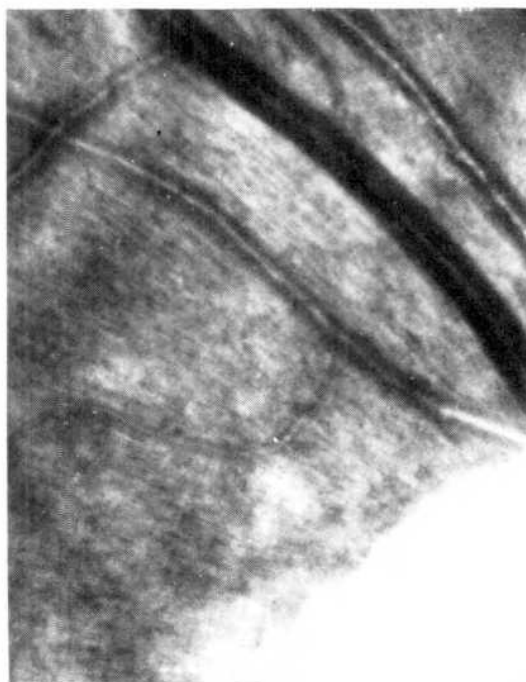
Fig. 3 Appearance of part of the peripapillary retinal nerve fibre layer in one and the same normal fundus, using different types of films and filters. Nominal camera magnification $3.4\times$, total magnification $40\times$. A. Colour print from Kodachrome 64, exposed in white light. B. Colour print from Kodachrome 64, exposed in green light (Wratten No. 40). C. Print from Tri-X Pan negative, exposed in green light (Wratten No. 40). Photographic paper grade No. 4. D. Print from Plus-X Pan negative, exposed in green light (Wratten No. 40). Photographic paper grade No. 4. E. Print from Technical Pan negative, exposed in white light, Photographic paper grade No. 1. F. Print from Technical Pan contact copy of the Kodachrome 64 slide shown in Fig. 3A. The colour slide was exposed in white light, and the contact copy in green light (Wratten No. 65A). Photographic paper grade 1. The large change in paper grade between Technical Pan (Fig. 3F) and Tri-X Pan and Plus-X Pan (Figs. 3C, D) gives an indication of the difference in contrast in the different films: Technical Pan is much more contrasty than the other films. The black-and-white prints were all produced in a condenser-type enlarger, without manipulation of exposure, or retouching.



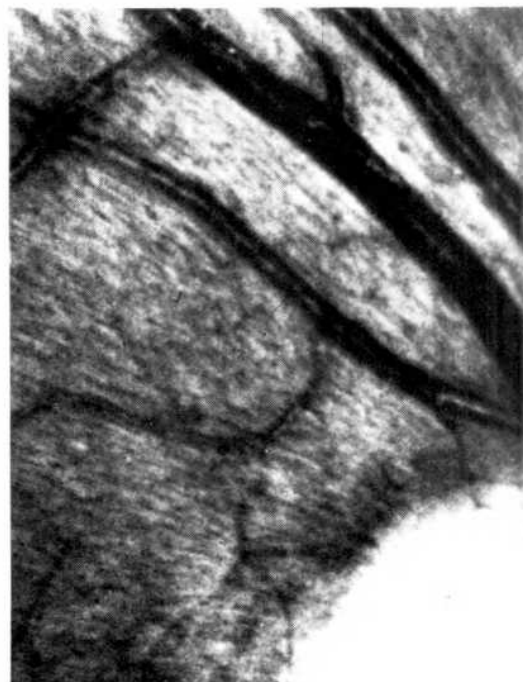
3C



3D



3E



3F

green filtering during photography with colour slide film appeared to have a limited value (Fig. 3B).

Black-and-white negative films in fundus photography. Two conventional black-and-white negative films were used in the fundus camera, namely Plux-X Pan and Tri-X Pan. As expected from the ratings (Table 1) and the results of the resolution study (Fig. 2), Plus-X Pan produced better detailed images of the peripapillary retinal nerve fibre layer, with a less disturbing graininess. With Plus-X Pan the visibility of the retinal nerve fibre layer was moderately enhanced when the Wratten No. 40 colour filter was introduced in the camera illumination beam. The effect was only marginal for Tri-X Pan (Figs. 3C and D). Three different developing procedures were tried with the Plux-X Pan film, namely Microdol 1+3, overdevelopment (15 min) in undiluted Microdol, and D-11 (1+1). The latter 2 produced more contrasty negatives but appeared to enhance granularity at the same time. The overall best results were obtained with the diluted Microdol developer.

Panatomic-X was not tried in the fundus camera because of its low light sensitivity.

The superiority of Technical Pan in the resolution study was not borne out at all magnification settings in fundus photography. Technical Pan has a higher sensitivity to red light than the other black-and-white films, resulting in enhancement of the choroidal pattern and attenuation of nerve fibre contrast when using white illumination light (Fig. 3E). Filtering the illumination beam with the Wratten No. 40 green filter reduced exposure so much that severely underexposed negatives were obtained at magnifications higher than $1.7\times$. However, finely detailed and contrasty images with very little graininess were obtained at $1.7\times$. At this setting the results were far superior to those obtained with the other 2 black-and-white films. The improved definition of peripapillary nerve fibre layer detail had to be traded against a poorer definition of details within the optic nerve head, however. This is due to the restricted exposure range of high contrast films (see further below).

One of the advantages with the Technical Pan negative film is that its contrast can be adjusted within wide limits, using different developers. HC-110 in different dilutions, and D-19 were tried. The best contrast within the retinal nerve fibre layer was obtained with 2 min of development in D-19, while longer development times led to impaired resolution and increased graininess. HC-110 produced softer negatives with a slightly better definition of disc detail.

At the $1.7\times$ magnification setting Technical Pan at present appears to be the film of choice for

black-and-white nerve fibre layer photography in green light. Unfortunately this film could not be used at higher magnifications, which often are necessary to obtain good resolution of fine nerve fibre detail. Plus-X Pan, developed in diluted Microdol, is a better black-and-white choice for higher magnifications.

Black-and-white copies of colour diapositives. The results described so far indicate that unfiltered colour slides constitute the best choice for ordinary fundus photography. Colour diapositive films produce natural-looking records with high resolution, extremely fine graininess, and a good contrast range. Their only disadvantage is the rather poor visibility of nerve fibre detail in comparison with filtered black-and-white films (Figs. 3A-D). A second stage production of contrast-enhanced black-and-white negatives from unfiltered colour diapositives could have several advantages, including: (1) elimination of the need to change film, filters, and illumination settings whenever nerve fibre records are desired; (2) elimination of the difficulties of focusing in faint, filtered light; (3) access in all cases to natural-looking primary records; (4) the possibility of processing slides obtained prior to the 'red-free era'; (5) the possibility of using low sensitivity films and low transmittance filters, without regard to the limited output power of fundus camera flash aggregates; and (6) freedom to choose films, filters, and developers on an individual basis in the seclusion of the dark-room.

Two methods of making black-and-white copies of unfiltered Kodachrome 64 slides were tried here.

A. Photographic reproduction at the 1:1 scale inevitably led to a loss of resolution. A variety of camera objectives were tried, mainly so-called macro- and microcamera objectives from major manufacturers, but also specialised reproduction objectives. The overall best results were obtained with a symmetrical apochromatic objective, namely, Rodenstock Apo-Rodagon 2.8/50 mm, at a working aperture of 5.6, on Technical Pan film. However, even with this objective and this film, there was a clear-cut loss in resolution when copying the slides from the resolution study (Table 2). Full resolution could be retained only by changing the scale of reproduction from 1:1 to 1:25:1, or larger. But the gain in resolution on magnification was offset by undesired cropping. Copying at higher scales without cropping involves considerable expense.

B. Contact copying with the simple device described above (Fig. 1) produced consistently better results than 1:1 photographic copying (Table 2). This was true for all black-and-white films and all filters. Copies of fundus colour slides on Plux-X

Table 2. Comparison of resolving powers in direct photography and copying

Test	Kodachrome 64	Tri-X Pan	Plus-X Pan	Panatomic-X	Technical Pan
Resolution at 1.7 × setting in fundus camera at high/low contrast levels (lines/mm)	56/48	40/34	40/34	—	56/48
Resolution in black-and-white copy of Kodachrome 64		Photographic copy	34/28	40/34	40/34
		Contact copy	40/34	48/40	56/48

Pan and Panatomic-X were highly similar and could not consistently be told apart. There was little loss of resolution in the case of Panatomic-X, slightly more so on Plus-X Pan. Microdol 1+3 was the best developer for both films. Overdevelopment in Microdol (15 min) and D-11 (1:1) produced better contrast but also a disturbing graininess. The very best results were obtained with Technical Pan, however. There was no detectable loss of resolution during contact copying on this film. Optimum nerve fibre layer contrast was obtained when developing for 2 min in D-19 (Fig. 3F).

Tri-X Pan was not of interest in this application because of its more pronounced graininess.

The various filters produced quite similar results with regard to nerve fibre bundle enhancement and differed primarily with regard to attenuation of choroidal detail. Wratten No. 65A and the interference filter produced equivalent negatives with good choroidal suppression; Wratten No. 40 admitted more choroidal detail, particularly in lightly pigmented fundi, making the definition of nerve fibre bundles somewhat softer.

In summary, contact copying unfiltered colour slides on Technical Pan, using Wratten No. 65A, and the D-19 developer, constitutes a simple and inexpensive technique for producing optimum nerve fibre bundle images, highly suitable as final records. The results produced in this way were considerably better than those obtained by the best technique for direct nerve fibre photography (Plus-X Pan exposed through Wratten No. 40, developed in Microdol 1+3). The latter technique produced less contrasty and much more grainy images. These disadvantages were offset to some extent by a somewhat better reproduction of disc detail. The very best reproduction of disc detail was obtained in unfiltered colour diapositives, however. A maximum of information was therefore obtained by analysing, side by side, a colour slide together with a filtered Technical Pan contact copy.

Printing black-and-white negatives. Negatives produced on Plus-X Pan, Tri-X Pan, and Panatomic-X could in general be printed on photographic paper of grade 1 or 2 without resorting to dodging or burning-in. This was not always the case with the

Technical Pan negatives: these were often too contrasty to print well even on grade 1 photographic paper. For printing, negatives of such a large contrast need to be complemented with positive masks (masks with a reversed density distribution). Such a mask has the effect of compressing the range of contrast. If the mask is unsharp, it has the paradoxical effect of enhancing sharpness of small details.¹² Unsharp masks are very useful also together with negatives of a more ordinary contrast range by virtue of the detail-enhancing effect. They also allow use of higher grade photographic papers.¹⁴ Unsharp masks are most easily produced by photographic copying at the 1:1 scale on Technical Pan film, interposing an opaque material in between the original negative and the camera lens. The loss of resolution inherent in the photographic copying is irrelevant in this instant. Actually, the mask should be unsharp enough to be devoid of nerve fibre bundle detail. An underexposed mask produces the best results. Full details of this technique have been given elsewhere.¹⁴

Discussion

The diameters of the individual axons that build up the retinal nerve fibre layer range normally between 0.6 and 2 μm .¹⁸ Fundus cameras cannot resolve such minute structures. Instead, photography depends on the convergence of axons on the peripapillary area, where the axons congregate densely enough to form a finely textured and slightly opaque layer that partially blurs out deeper structures. Texture is a surface characteristic attributable to the formation of bundles of nerve fibres. These bundles continually change in diameter because of the tendency of individual axons to weave back and forth and up and down.¹⁰ Texture is therefore defined by extremely fine detail of low contrast. It is difficult to assign meaningful numerical values to texture and opacity, but it is clear that maximal resolution and maximal utilisation of contrast are required for successful nerve fibre layer photography. Therefore optimum results require precise focusing, maximum utilisation of contrast, and the use of a

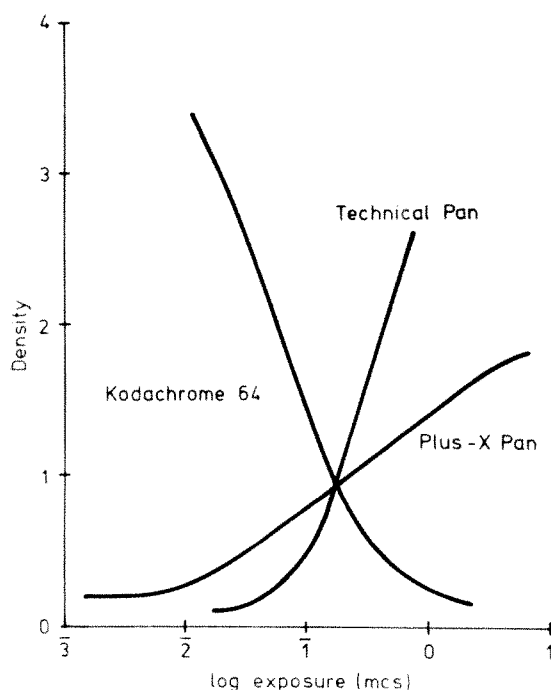


Fig. 4 Characteristic curves for some films used in this study. Redrawn from the manufacturer's data.

fine-grain film that does not fall short of the resolving power of the eye-and-camera system.

The optimum choice of film was extensively treated above and may need little additional comment here. But a few comments concerning high contrast films and their properties may be offered. In high contrast films the relationship between exposure and film density (the 'characteristic curve'¹⁶) is much steeper than in ordinary films: a small increment in exposure causes a much larger increment in density. This effect is won by extending the useful density range, and compressing the useful exposure range (Fig. 4). Small differences in exposure, like those produced by adjacent nerve fibre bundles, cause only small variations in density in ordinary films. High contrast films amplify these small-scale variations, resulting in enhanced visibility of fine, low contrast detail. The gain in contrast has to be paid for. The restricted exposure range makes simultaneous recording of disc and nerve fibre detail somewhat difficult, and the images tend to become too contrasty to print directly (precisely as x-ray films). To avoid degradation in printing, high contrast films are best used as they are, i.e., as transparencies, and viewed under magnification. The restricted exposure range cannot be circumvented, however. Fortuitously, the best

technique for producing high contrast nerve fibre layer records (copying unfiltered colour slides on to high contrast film, using filtered light) ensures availability of a natural-looking primary record. A maximum of information is obtained by analysing the colour slide and the nerve fibre transparency side by side.

Correct exposure is important for high quality photography. Both underexposure and overexposure lead to loss of information. Both high contrast black-and-white films and colour slide films are very sensitive to aberrations from correct exposure. It would be highly advantageous if the camera manufacturers could offer exposure sensing devices that could control the duration of the flash, akin to the automatic flash devices used for conventional photography. Limitation of illumination is desirable also for minimising the risk of retinal damage from light. Although the levels ordinarily used during fundus photography may fall short of critical levels,²⁰ it is always sound to focus in the faintest, useful light, and to avoid low sensitivity films. Furthermore, excessive bleaching of rhodopsin impairs nerve fibre bundle contrast.²¹

Concerning resolution, little can be done to improve on existing fundus cameras, except for ensuring that the camera is clean, properly adjusted, and carefully focused. Focusing is a notorious problem in fundus photography.⁵ Instrumental aids have been described, but their value for photographing the nerve fibre layer has not yet been explored.^{3,6} The difficulties of manual focusing are usually attributed to variations in the photographer's accommodation. While such variations undoubtedly may contribute to focusing difficulties, it appears more likely that the main problem is caused by the photographer's lack of knowledge of his degree of instrument myopia (or 'the intermediate dark focus of accommodation'²²). The dark focus of accommodation can be determined only by using special equipment, but it is possible to obtain a good approximation in the following way. 1.7 D (=the average normal value of instrument myopia according to Leibowitz and Owens²²) is subtracted from the photographer's refraction. The resulting value indicates the starting setting of the camera's ocular. After focusing in adequate light for a clear fundus image a few photographs are taken of one and the same eye at this ocular setting. Instrument myopia is then bracketed by refocusing and photographing after ± 0.5 and ± 1.0 D changes in ocular setting. Inspection of the photographs then shows the optimum setting of the ocular for future photography.

The depth of focus is inversely proportional to the degree of camera magnification. Although lower

magnifications are more tolerant against focusing errors, higher magnifications give images with better detail. A good compromise between resolution, depth of focus, and size of field, seems to occur around 3 to 4 $\times$.

Uncorrected astigmatism is detrimental to fundus photography. Even 0.5 D of astigmatism produces noticeable blur. It is deplorable that most manufacturers of fundus cameras do not offer astigmatism compensation devices. Such devices are indispensable for good nerve fibre layer photography also in patients without astigmatism in central vision. Astigmatism arises as soon as the camera is disaligned with the optical axis of the eye.²³ Such disalignment is usually required during photography of the peripapillary nerve fibre layer.

Discussions of ways and means for improving clinical nerve fibre layer photography have largely centered on the utility of various filters in the camera's illumination beam. To the casual ophthalmoscopist this may appear surprising, as the nerve fibre layer usually appears as a whitish or greyish structure. This layer apparently reflects light from all parts of the spectrum to about the same extent. Maximum information should then be retained by using full spectrum illumination. The earlier notion that the nerve fibre layer is opaque to light of short wavelengths^{7, 24} has been refuted.²⁵ The rationale for filtering may relate to other factors, including nerve fibre layer translucency, and film properties. The relative enhancement of nerve fibre bundles in unfiltered black-and-white negatives, as compared to unfiltered colour slides, suggests that it is reddish retroillumination from deeper structures that attenuates the contrast of the nerve fibre layer in colour films. Most black-and-white films have a much poorer sensitivity in the red end of the spectrum than colour films. Filtering black-and-white films with a Wratten No. 40 gelatin filter enhances definition of the nerve fibre layer in proportion to the film's sensitivity to red: the effect is only marginal for Tri-X Pan, more pronounced for Panatomic-X and Plus-X Pan, and dramatic for Technical Pan. As mentioned above, the precise characteristics of the filter appear to be relatively unimportant. An expensive interference filter is not necessarily better than a simple gelatin filter. Orthochromatic films may need no filtering at all.¹²

The optimisations analysed in this study do not solve all the problems associated with clinical photography of the retinal nerve fibre layer. Patients with optical imperfections, thinner than normal nerve fibre layers, or a poor background pigmentation, still remain difficult to photograph. It is difficult to see ways of circumventing these problems. The texture of the retinal nerve fibre layer could

possibly be enhanced by using indirect illumination. Fundus cameras with better resolving powers might be of aid. Holographic photography,²⁶ special methods of film development,¹³ optical contrasting,²⁷ and computerised spatial frequency filtering²⁸ might also prove useful.

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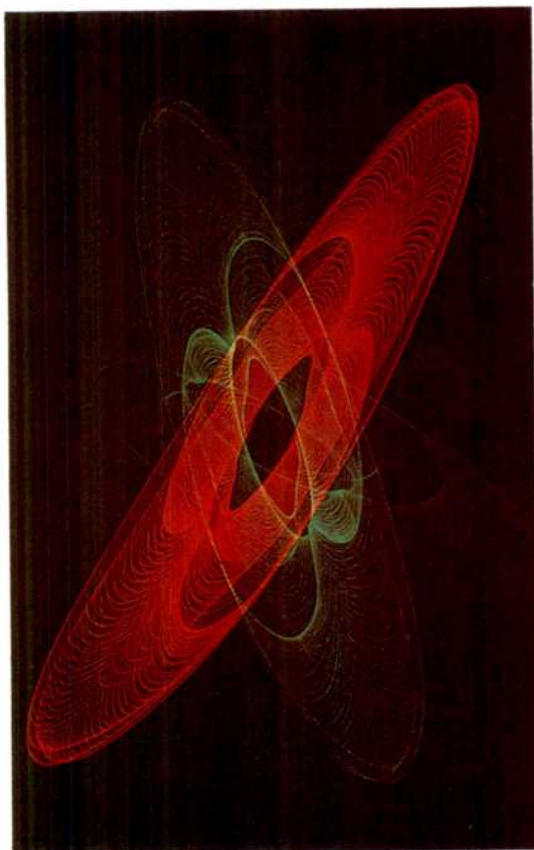
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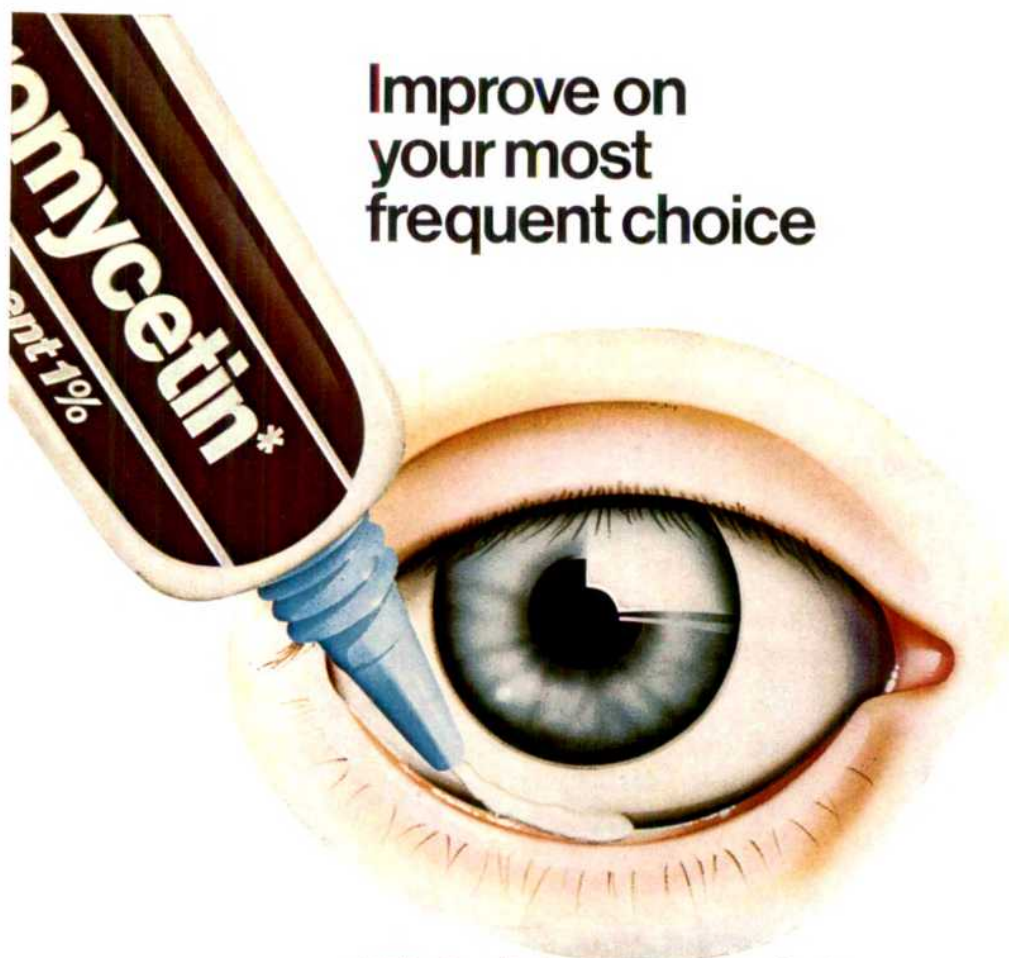
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P175-UK-Feb 80

PARKE-DAVIS

Acquired medullated nerve fibres

G. S. BAARSMA

From the Eye Department, Erasmus University, Eye Hospital, Rotterdam

SUMMARY Myelination of nerve fibres normally stops at the lamina cribrosa. When it does proceed beyond the lamina cribrosa, it is believed to do so shortly after birth. A patient is recorded in whom medullated nerve fibres developed in the retina during adult life.

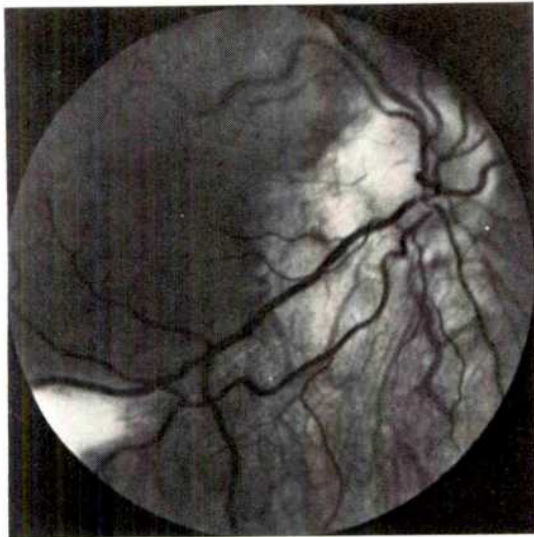


Fig. 1 *Striated whitish lesion in right eye.*

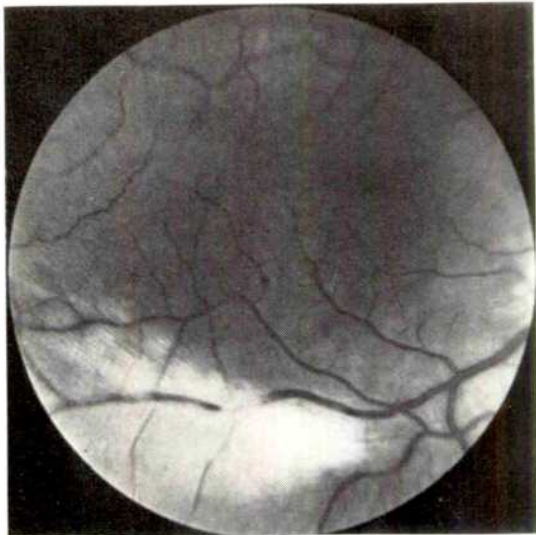


Fig. 2 *Striated whitish lesion in right eye.*

Case report

A 23-year-old male experienced blunt trauma to his right eye from a blow with a fist. In the acute stage signs of a slight contusion were present. The fundus of the right eye showed a striated whitish lesion along the inferior temporal artery (Figs. 1 and 2), which could only be interpreted as being medullated nerve fibres. Fluorescein angiography revealed no other abnormality. The patient was a mild diabetic controlled by diet, and his right fundus had been photographed 7 years earlier. The medullated retinal fibres were not detectable on the earlier photographs (Fig. 3) nor were they recorded in the patient's file. There was no change in corrected visual acuity of the right eye over this period.

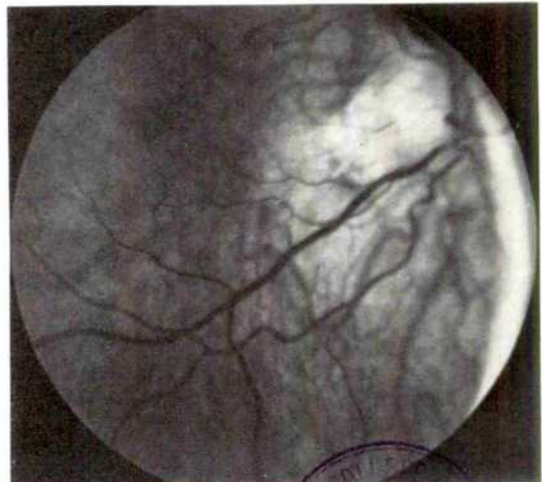


Fig. 3 *Earlier photograph of right eye.*

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Benign familial fleck retina

SURA F. SABEL AISH AND BASEM DAJANI

From the Jordan University Hospital

SUMMARY A family with a benign form of fleck retina is described. Seven out of 10 siblings were affected. The consanguinous parents were both normal. The fundi were massively invaded by lesions which appeared as discrete, bright white or yellow flecks situated well behind the retinal blood vessels. The macula was always free. Fluorescein studies revealed a healthy macula and retinal and choroidal blood vessels. The relationship of this benign form to the other forms of fleck retina is discussed.

Massive mosaic hyaline excrescences along the cuticular layer of Bruch's membrane, leading to the appearance of multiple deep yellow to yellowish white lesions of variable size and shape in the fundi have been well known for more than a century.¹⁻³ Many forms of this condition have been described with different findings, prognosis, and inheritance.⁴⁻¹⁵

Krill^{16,17} regarded all these conditions as fleck retina diseases. He then classified them into 4 groups: fundus albipunctatus, fundus flavimaculatus, familial drusens, and fleck retina of Kandori. This classification with subgrouping according to the severity of the condition seemed to bring order into the confusion that had lasted for a century.

In this paper we present a family with flecked retina, with typical funduscopy picture and normal visual findings. We suggest they belong to a fifth group—benign familial fleck retina.

Patients and methods

This was an Arab Palestinian family residing in Amman-Jordan. There were 10 children. The parents are first cousins. All 12 members of the family were studied. The parents had normal vision and fundi. Seven out of 10 children had flecked retina (Fig. 1). The affected children had undergone the following ophthalmic investigations: Refraction tests and assessment of visual acuities, dark adaptometry, central and peripheral visual fields, funduscopy along with white light photography, and fluorescein angiography. Examination of the patients included a full blood picture; blood

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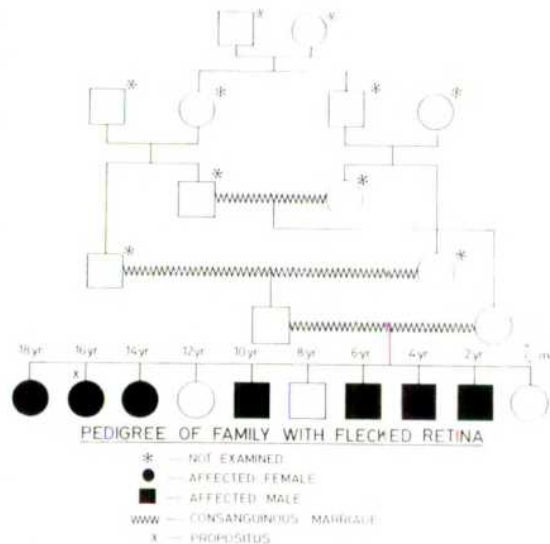


Fig. 1 The pedigree of the family.

sugar, cholesterol; protein electrophoresis; and skull x-rays.

CASE 1

The proband was a 16-year-old girl who presented in 1977 with headaches. She gave no history of ophthalmic or systemic disease.

On examination her visual acuities were 6/18 corrected to 6/6 with -1.00 DS in either eye. The anterior segments of both eyes were normal, and the intraocular pressures were within normal limits. Central and peripheral visual fields did not show any abnormalities, and dark adaptometry was normal. Funduscopy showed that in both eyes

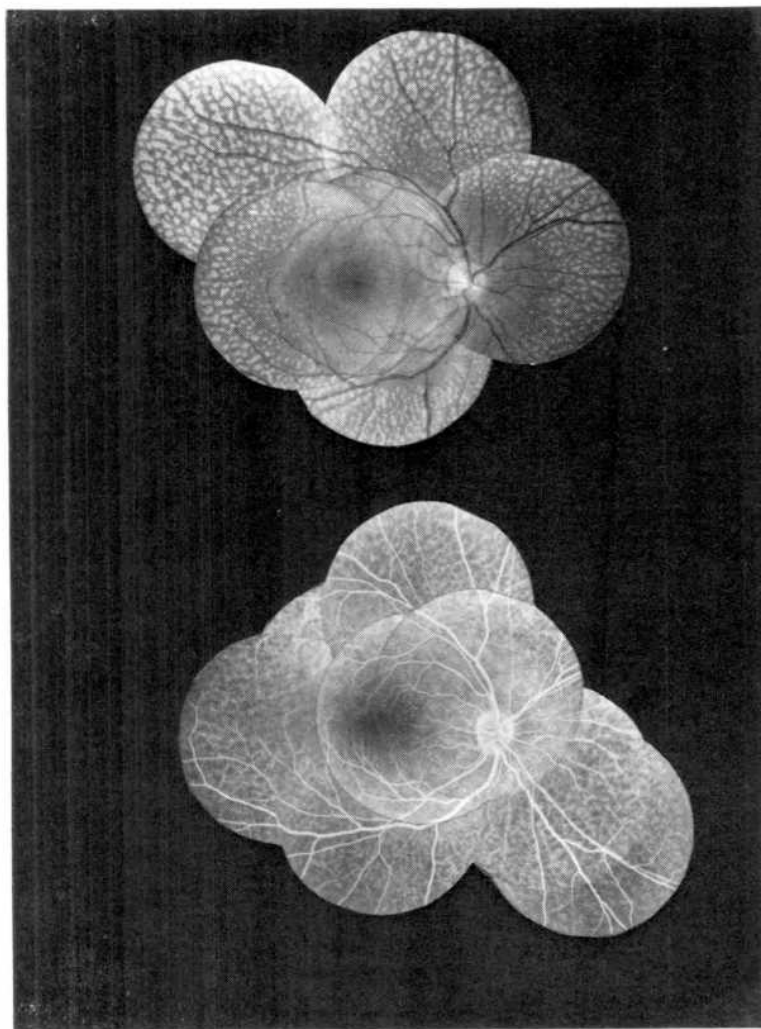


Fig. 2 Above: White light photograph demonstrating fleck retinal dystrophy in case 1 (the propositus). Central areas are spared. Below: Fluorescein angiography of the same eye. Notice that the macula is the only nonhyperfluorescent area.

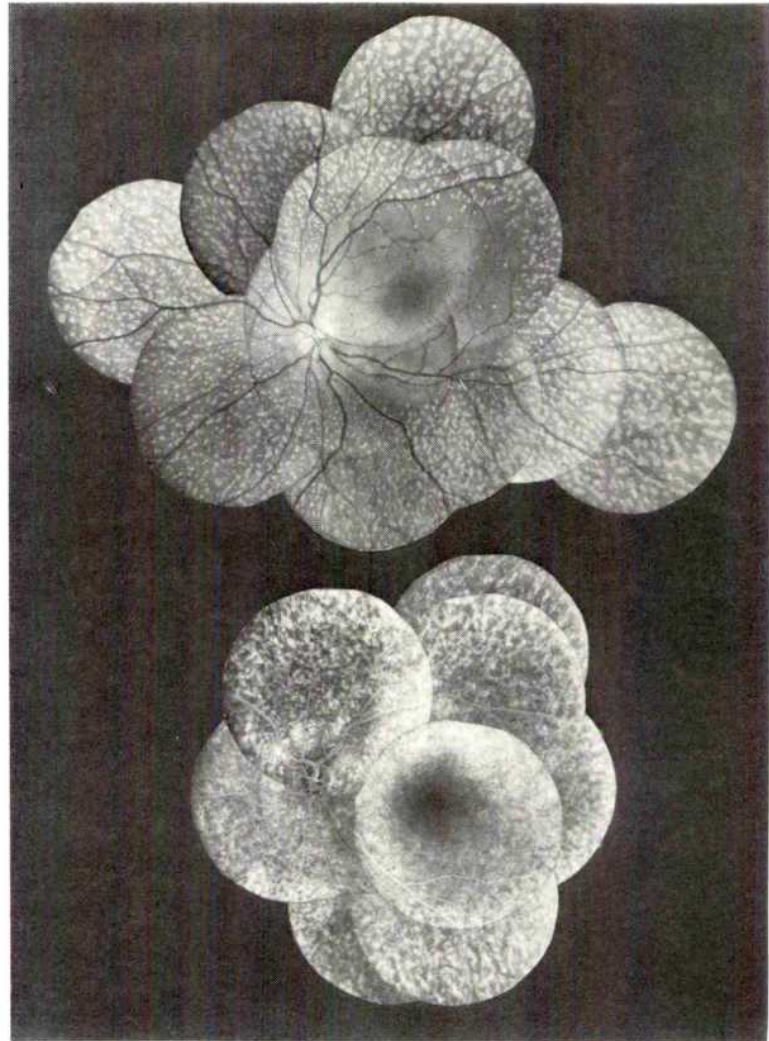
the fundi were invaded by an enormous number of bright white and sometimes yellowish white flecks of variable size and configuration, arranged in a concentric pattern around the posterior fundus and sparing the optic disc, macula, papillomacular area as well as 1–2 disc diameters circular region surrounding the disc and macula. They spread everywhere in the equator and mid and extreme periphery of fundus. The more centrally located flecks appeared sparse, small, round, and dot-like. Others of larger size in the equatorial and peripheral areas varied in shape, being, round, elongate, pisciform, star-shaped, and sometimes circular. The flecks were always discrete, well defined, with almost sinuous margins and a flat or prominent surface. They appeared to be solid and well behind the

retinal vascular tree. Throughout the fundus they showed the same mosaic appearance. They spared no area in the periphery. No pigmentary disturbances, calcification or conglomeration was observed, nor were choroidal vessels observed.

Follow-up 1 year later gave the same funduscopy findings, with 6/6 corrected visual acuity in either eye. Headaches had disappeared, visual fields were again normal, and there was no delay in dark adaptation.

Fluorescein angiography carried out at this time showed that apart from the macula the whole fundus was hyperfluorescent, including the central areas which appeared free of flecks on funduscopy and white light photography. This indicated there was no close correlation between the site of the

Fig. 3 Above: Plain fundus composite photograph illustrating the distribution of flecks in case 2. The flecks involve more central areas than those in case 1. Below: Fluorescein angiography to the same eye.



flecks and the hyperfluorescent areas, particularly in the central part of the fundus (Fig. 2).

CASE 2

The eldest sister of the propositus was 18 years old. She gave no history of systemic or ophthalmic trouble.

Visual acuity in both eyes was 6/6. Her visual fields and dark adaptometry were normal. The fundi were extensively invaded by flecks like those seen in case 1. The disc, macula, and paramacular area bordered by the upper and lower temporal retinal vascular branches were the only areas that were spared (Fig. 3). Small, round, dot-like flecks were distributed nasally above and below the disc, while the equatorial and midperipheral areas of the

fundi were invaded by much larger fleck lesions with irregular configurations, mainly longitudinal in shape. The most peripheral parts of the fundus were invaded mainly by linear flecks. The results of fluorescein angiography were comparable to those seen in the propositus. The only nonfluorescent area was the macula (Fig. 3).

CASE 3

A 14-year-old boy, brother of the propositus. His corrected visual acuities were 6/6. His visual fields were normal, and he did not show any defect in dark adaptation. The fundi were very extensively invaded by fleck lesions, comparable in shape and size to those in the propositus. But in this case, apart from the disc and macula, no other areas were

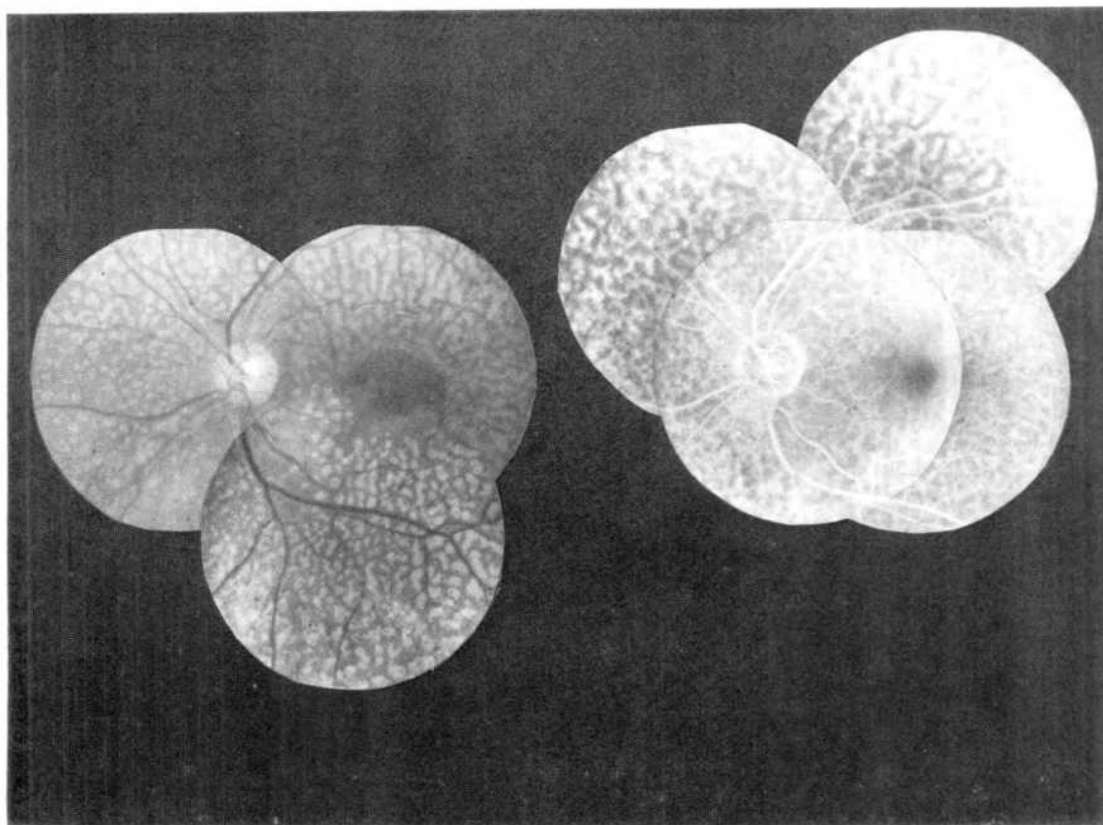


Fig. 4 Left: White light fundus composite photograph of the left eye of case 3. Right: Fluorescein angiography of the same eye.

spared (Fig. 4). As in the previous cases, fluorescein angiography showed hyperfluorescence of the whole fundi apart from the macula itself, with a normal vascular tree (Fig. 4).

CASE 4

A 12-year-old boy, brother of the proband. This child was also healthy, with 6/6 visual acuities and normal visual fields and dark adaptometry. Both his eye grounds were affected with fleck lesions comparable in shape, size, and distribution to those in the proband, as seen by funduscopy, fundus photography, and fluorescein angiography (Fig. 5).

CASE 5

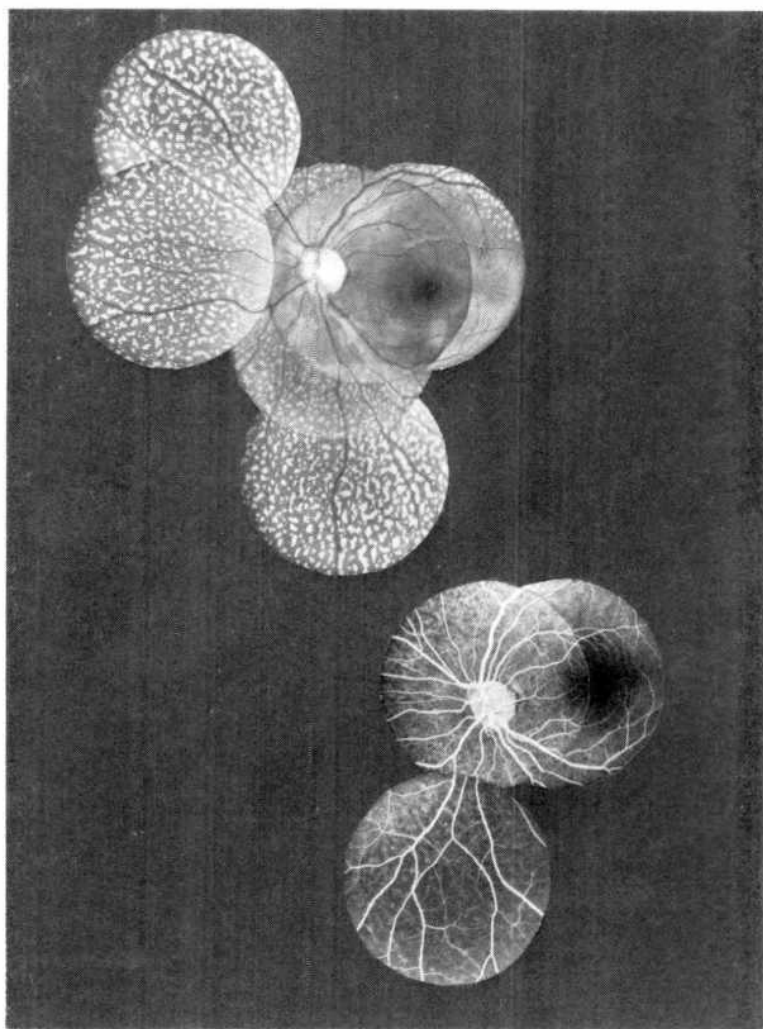
A 6-year-old brother of the proband. He had 6/6 uncorrected visual acuities with normal visual fields and dark adaptometry. Only the mid and extreme periphery of the eye grounds were invaded by small, dot-like, round fleck lesions. Some appeared to be of the same shape as those found in the pre-

vious cases but never of the same size. The disc, macula, and retinal as well as choroidal blood vessels were normal. Fluorescein angiography revealed a rather uniform hyperfluorescent fundus apart from the fleck-free macular area (Fig. 6).

CASE 6

A 4-year-old boy, brother of the proband. As in the previous cases he had 6/6 vision in both eyes, and examination of the anterior segments of both eyes showed nothing abnormal. Funduscopy of both eyes revealed symmetrical involvement, with fine fleck lesions scattered everywhere beyond the central fundus. The flecks appeared immature in comparison with those seen in the older sisters and brothers. Discrete and sparse along the central border of the involved areas, they were mainly round in shape. Fluorescein angiography revealed hyperfluorescent fundi except for the macula itself. The retinal and choroidal blood vessels were normal (Fig. 7).

Fig. 5 Above: *White light fundus photography*. Below: *Fluorescein angiography to left eye of case 4*. Here the pattern and distribution of flecks are rather similar to those of the *propositus*.



CASE 7

A 2-year-old boy, brother of the *propositus*. Fundoscopy showed the same appearance as in case 6, except that the fleck lesions appeared smaller, fainter, and sparser; they were situated mainly in the peripheral fundus (Fig. 8). Fluorescein angiography could not be undertaken. The child appeared emmetropic, with normal day and night vision.

Discussion

The 7 cases presented here are characterised by multiple whitish or yellowish white fleck-like deposits deeply situated in the retina well behind the retinal vascular tree. They varied in size and configuration, being round, pisciform, star-shaped,

and linear. No vascular changes in either retina or choroid and no abnormalities in the central fundus were observed. Nor could pigmentary disturbances or secondary calcifications be seen among the fleck-like lesions. Apart from some differences in size and shape of the flecks and slight variations in the pattern of their distribution in the juxtapapillary area, these 7 cases seem to constitute a uniform fleck retina dystrophy.

Clinically there was no night blindness or any delay in dark adaptation. The fundal lesions in the younger patients were clearly immature when judged by their size, density, concentration, and shape in comparison with those of the older patients. However, the findings at fluorescein angiography did not differ with age of patient. These observa-

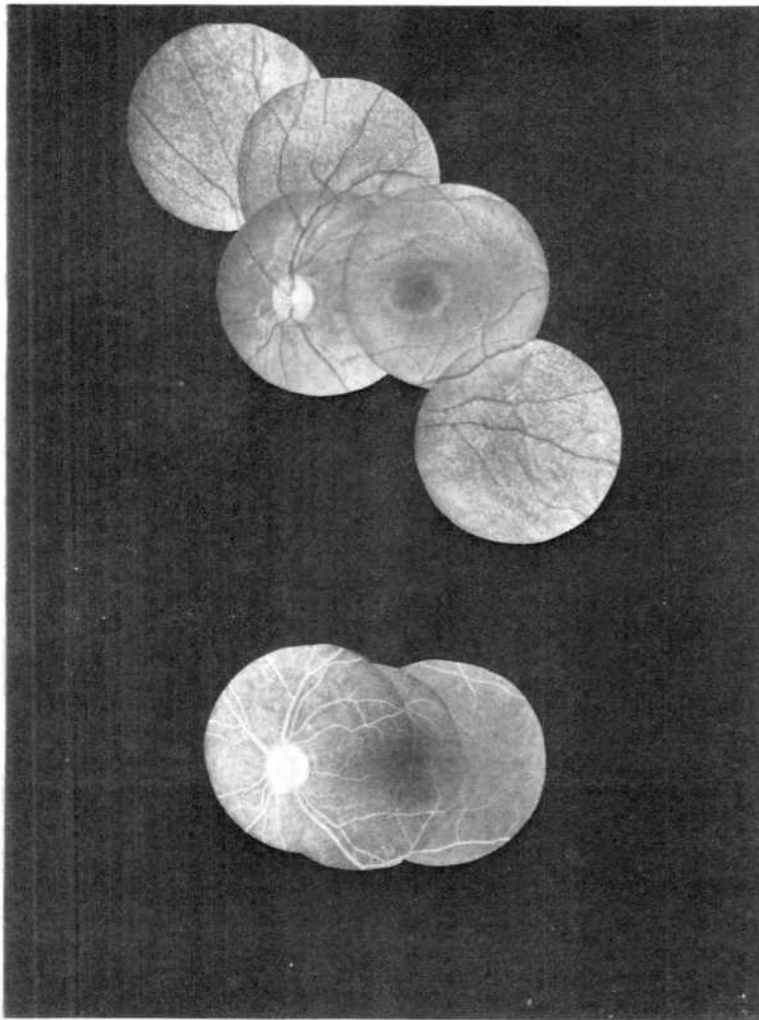


Fig. 6 Above: *White light* photography. Below: *Fluorescein* angiography. Left eye, case 5. Notice the fine immature flecks which are studded in the paracentral and peripheral area.

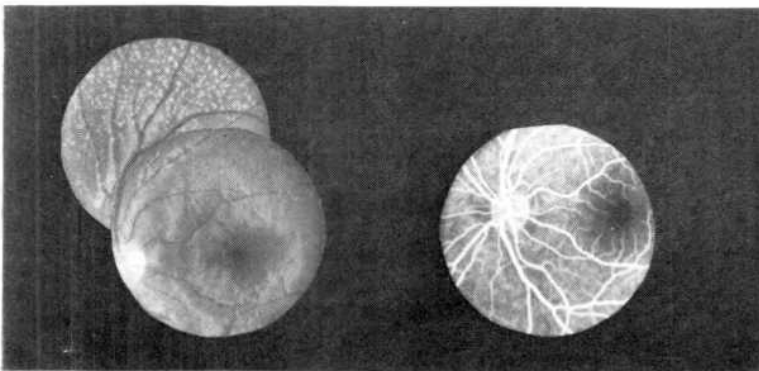


Fig. 7 Left: *White light* fundus photograph of left eye in case 6, showing the small fine flecks dystrophy extending beyond the central areas. Right: *Fluorescein* angiography of same eye.

tions, together with the fact that there was hyperfluorescence of the fleck-free area as seen with fundoscopy and white light photography, suggest that involvement of Bruch's membrane antedates the appearance of the flecks.

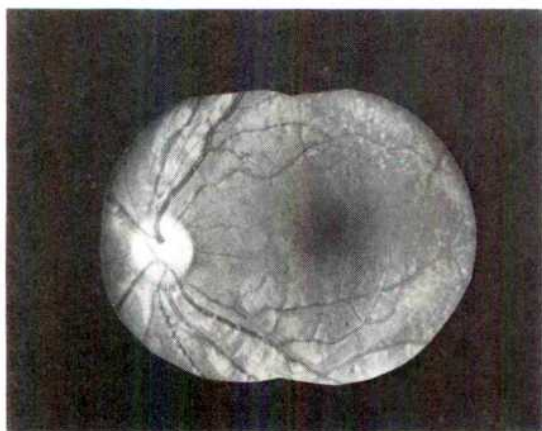


Fig. 8 Fundus white light photograph showing some discrete, fine, dot-like flecks scattered in the peripheral fundus of left eye in case 7.

The main features of the different types of flecked retina disorders reported in the literature are summarised in Table 1. We consider the family reported here to be a separate entity, benign familial fleck retina. In contrast to all previously reported cases of fleck retina disorders our cases showed no disturbance of visual functions attributable to the disorder during a 3-years follow-up. It is obvious that our family cannot be considered as familial drusen or fundus flavimaculatus. The macular involvement, calcifications, choroidal involvement, and visual function disturbances reported in these conditions are different from what was seen in our family.

The distribution of the flecks in our cases may be similar to that of fundus albipunctatus, but their shape is different. In addition, the fact that none of our cases had any disturbance of visual function puts them in a separate entity. When compared to cases of the fleck retina of Kandori our cases show more extensive involvement of the fundus, with flecks of different shape and size that show no conglomeration.

We suggest that benign familial fleck retina is inherited as an autosomal recessive condition. This is

Table 1 Classification of fleck retina disorders

Fleck retina disease	Changes in fundi	Functional disturbances	Mode of inheritance
Fundus albipunctatus ^{4, 6, 18, 20}	Discrete uniform white dots. Distribution: over the whole fundus greatest density at midperiphery. No macular involvement. No pigmentary disturbances or secondary calcification	Night blindness. Dark adaptation: normal, slow or monofunctional (only cone threshold)	Autosomal recessive Autosomal dominant ²¹
Fundus flavimaculatus ^{9, 11, 14}	Round, linear, or pisciform lesions. Distribution: limited to the posterior pole, or extends to the equator. Macula is involved. Network atrophy of retinal pigment epithelium. Choroidal vascular atrophy	Central visual loss, colour vision loss, photophobia, paracentral scotoma, slow dark adaptation	Autosomal recessive ^{17, 11, 21, 22}
Familial drusen ^{21, 22}	Round or oval lesions in almost grape-like clusters. Distribution: concentrated in the posterior polar region. Pigmentary disturbances and secondary calcifications. Macula is almost always involved, may appear oedematous or haemorrhagic	Loss of vision during progressive stages, central scotoma slow dark adaptation	Autosomal dominant ^{19, 22, 24-26}
Fleck retina of Kandori ^{7, 20}	Irregular flecks with great variability in size. Distribution: in the equatorial or between the equatorial and macular region with tendency for confluence. No macular lesions. Disturbance of pigment epithelium	Some night blindness. Initially delayed dark adaptation, recovers to normal value after 30-40 minutes in the dark	Autosomal recessive
Benign familial fleck retina	Round, linear, or pisciform. Distribution: in the whole fundus except the disc and macula. No macular lesions. No tendency for confluence. No pigmentary disturbances	No disturbance of visual function (no symptoms)	Autosomal recessive

supported by the fact that both sexes were involved and that both parents were free of the disease.

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Posterior ocular abnormalities after irradiation for retinoblastoma: a histopathological study

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SUMMARY Radiation-induced ocular lesions in the posterior eye and orbit were investigated in 33 surgical specimens of patients with retinoblastoma. The eyes were obtained from children 7 months to 6 years of age. Seventeen eyes were irradiated; 16 eyes had not received irradiation and served as controls. The majority of the irradiated eyes were treated with 6000 rads of external beam radiation. They were removed at a mean of 23 months after radiotherapy. All specimens were examined simultaneously by 2 observers without knowledge of treatment and analysed for the presence or absence of 15 lesions. The most consistent lesions in the irradiated eyes were abnormalities of the retinal vessels (11 of 17 eyes) and striking changes in the ciliary arteries (13 of 17 eyes). The retinal vessels showed thickening of the wall, often caused by deposition of fibrillary material, sometimes with fibrin deposits. The most consistent lesion was myointimal proliferation with narrowing of the ciliary arteries. Lesions of the central retinal artery were less common but occurred only in irradiated patients.

Radiotherapy is effective and valuable for diseases in or near to the eye; however, its usefulness is limited by the possibility of ocular radiation injury. Damage to the anterior structures of the eye, especially the lens and cornea, by low doses of radiation (in the range of 1000 rads) has been well documented,¹ whereas it has been considered that the posterior parts of the eye tolerate higher doses.² Damage to the retina and optic nerve can occur with fractionated radiation above 6800 rads.³ Changes in the ciliary vessels have not, to our knowledge, been described. We have examined the histological changes in a series of eyes that were removed after external radiotherapy for retinoblastoma and have found damage in the posterior ciliary vessels, optic nerve, and retinal vessels.

Materials and methods

Thirty-three eyes from patients with retinoblastoma were examined; 17 eyes had been irradiated and subsequently enucleated, and 16 eyes had not been

irradiated and served as controls. All specimens were examined simultaneously by 2 observers (PRE, LFF) in a double-head microscope, without knowledge of treatment, and analysed for the presence or absence of 15 morphological abnormalities. The severity of myointimal proliferation of the posterior ciliary arteries was graded in a scale of 0 (normal) to 4 (complete luminal obstruction). Five normal eyes from necropsies of children were also examined for the same lesions.

Standard axial sections of the entire eyeball embedded in paraffin as well as transverse sections of the optic nerve were used. In addition to haematoxylin and eosin the stains used included periodic acid Schiff (PAS), Verhoeff's elastic (EVG), Fraser-Lendrum method for fibrin, Alcian blue method for acid mucopolysaccharides, Luxol-fast blue for myelin, and the Bielschowsky method for nerve fibres.

The irradiated eyes had been enucleated because of uncontrolled tumour growth, pain from neovascular glaucoma, or inability to examine the eye because of vitreous haemorrhage. Most of the eyes came from patients who were part of a previous study of visual function following radiotherapy.⁴

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The irradiated eyes had been treated by megavoltage irradiation generated from a 6 MeV medical linear accelerator with doses of 5200 to 6000 rads given in 200–250 rad fractions over approximately 6 weeks. The one exception to this dose occurred in an eye enucleated 2 weeks after initiation of treatment, having received only 2250 rads. Five eyes of 5 patients had more than 1 course of radiation, which significantly increased the total dose to as much as 13 000 rads; 4 of these patients were also given intra-arterial triethylenemelamine and 1 eye had a ^{125}I implant. Several eyes were treated by photocoagulation or cryotherapy.

With the exception of one 6-year-old child, the patients' ages at the beginning of radiotherapy ranged from 7 months to 2 years. The age range of the nonirradiated controls was comparable. The interval from the first day of radiotherapy to enucleation was 2 weeks to 34 months (mean 23 months).

Results

There were clear differences between the irradiated and nonirradiated eyes (Table 1). The most consistent changes were in retinal vessels and extraocular posterior ciliary arteries. Cataract and neovascularisation of the iris were also seen in irradiated eyes. However, the comments that follow refer only to the important lesions in the posterior part of the eye.

Retinal vessel changes were seen in 11 of 17 irradiated eyes. Marked thickening of the arteriolar and capillary walls occurred, both in residual tumour and in areas away from the tumour. Most often the thickening was caused by the accumulation in the entire wall of a fine fibrillary material

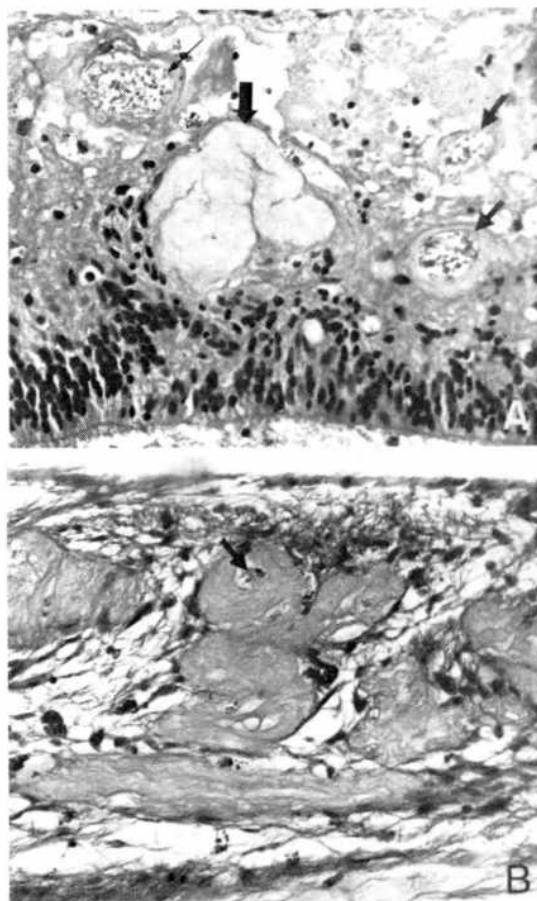


Fig. 1 Perpendicular sections of retina. A: Eye resected 6 months after 6000 rads/25 fractions/44 days. Notice marked atrophy of the outermost layers and abnormalities of vessels. There is irregular wall thickening and dilatation of capillaries (small arrows). In the centre (large arrow) is an arteriole totally replaced by convoluted, fibrillary material. Its lumen is no longer recognisable. B: Specimen obtained 7 months after 5950 rads/29 fractions/43 days. There is severe atrophy of all retinal layers. All vessels in this field are markedly thickened by fine fibrillary material which is in or outside the vessel walls. The remaining lumen can be recognised in some (arrow). (Haematoxylin and eosin, $\times 200$).

Table 1 Posterior ocular histological changes associated with radiotherapy

	Retinoblastoma		Normal
	Radiation	No radiation	
Number of eyes	17	6	5
Lesions of retinal vessels (away from tumour)	11	0	0
Myointimal proliferation in central retinal artery	4	0	0
Myointimal proliferation in posterior ciliary vessels	13	0	0
Optic nerve axonal and myelin loss	13	11	0
Diffuse	6	1	
Segmental	1	6	
Diffuse and segmental	6	4	

(PAS-negative) which narrowed the lumen and appeared to progress to occlusion (Figs. 1, 2). This material replaces the wall and may be partly extravascular. Fibrin was demonstrated in the wall of a number of vessels by the Fraser-Lendrum or the phosphotungstic acid-haematoxylin (PTAH) stains (Fig. 2). Fibrin was also found outside of the vessels in the adjacent retinal stroma. Extensive vascular

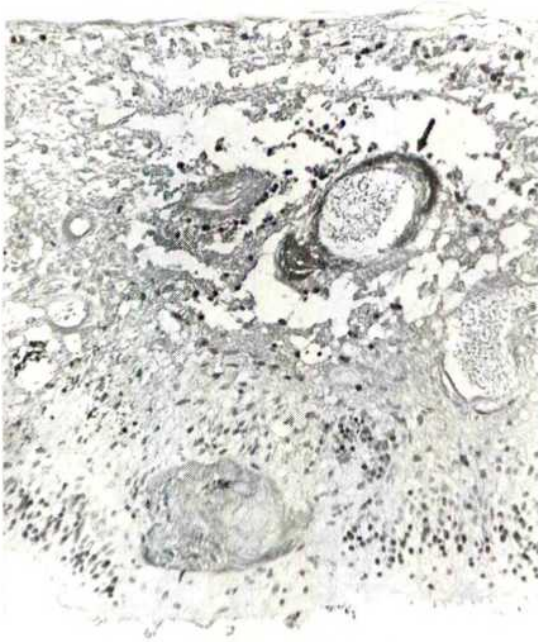


Fig. 2 Section of retina from the same eye described in Fig. 1A. Notice totally obliterated vessel in the outer retina. One of the vessels in the inner layers (arrow) shows not only dilatation but also severe fibrinous exudate in the wall, which appears black (red-purple in the histological preparation). (Fraser-Lendrum stain, $\times 135$).

proliferation into the vitreous was present in 2 eyes. There were no retinal vessel changes in the control nonirradiated eyes.

The posterior ciliary arteries in the region of the anterior optic nerve and posterior sclera showed abnormalities in 13 of the 17 irradiated eyes and in none of the unirradiated eyes. These changes were present as early as 5 months after initiation of irradiation. Myointimal proliferation, either concentric or eccentric, encroached on the lumen of arteries of 100 μm to 200 μm in diameter and at times obliterated the lumen completely (Figs. 3, 4). Enlarged endothelial cells and thick elastic lamina were also seen (Fig. 4). Although these changes were obvious in the larger ciliary arteries, adjacent veins and venules, as well as smaller arterioles and capillaries, were usually normal. Occasionally similar abnormalities were present in arterioles in the optic nerve sheath or in the optic nerve itself; however, capillaries in the optic nerve usually appeared unremarkable. Myointimal proliferation of the central retinal artery, without occlusion, was found in 4

eyes enucleated 5, 12, 17, and 23 months after radiation (Fig. 5).

Optic nerve atrophy was observed in nonirradiated as well as in irradiated eyes. It was characterized by a decrease in the diameter of the nerve and loss of axons and myelin. The distribution of this lesion, however, was not the same in both groups. Diffuse atrophy (Fig. 6) was seen preferentially in the irradiated eyes; a segmental atrophy (Figs. 7, 8) was seen preferentially in nonirradiated eyes (Table 1).

The choroid was difficult to evaluate because of the large number of collapsed vessels, adjacent to each other; we did not identify obvious choroidal radiation-induced changes. The retinal pigment epithelium showed areas of atrophy and areas of hyperplasia in both irradiated and nonirradiated eyes. The sclera also had no radiation-related abnormalities.

There was no consistent relationship between the severity of myointimal proliferation in the ciliary arteries and the age of the patient, the radiation dose, or the length of the interval from the first day of radiation to enucleation. The 5 eyes which had no changes in the posterior ciliary arteries were enucleated one-half, 5, 7, 7, and 13 months after initiation of radiotherapy. All eyes removed later had changes; however, damage to the posterior ciliary arteries was also seen in 3 eyes removed 12 months or less after radiotherapy.

Vascular injury was seen in eyes at the low as well as the high end of the dose range. One eye showed

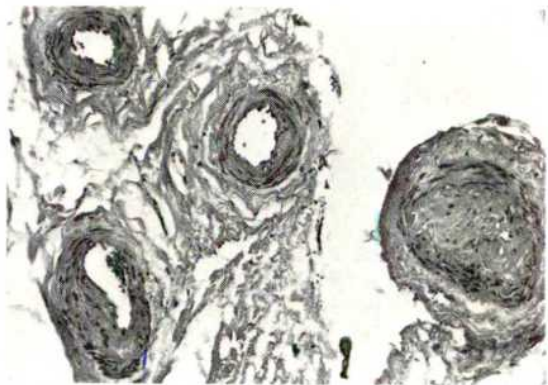


Fig. 3 Transverse sections of posterior ciliary arteries from eye resected 2 years after 6000 rads/25 fractions/44 days. The arteries in centre and left upper corner are essentially normal. There is eccentric myointimal proliferation with slight narrowing of vessel in left lower corner. The artery on the right is totally occluded by myointimal proliferation. This case illustrates the random distribution of radiation-induced lesions. (Haematoxylin and eosin, $\times 90$).

damage after 5200 rads and several after 6000 rads. All eyes that had multiple courses of radiation had vascular damage, usually severe. The eye enucleated after only 2250 rads (2 weeks after the initial dose) showed no vascular damage.

Discussion

The most interesting findings in this study were the abnormalities in the posterior ciliary arteries. We

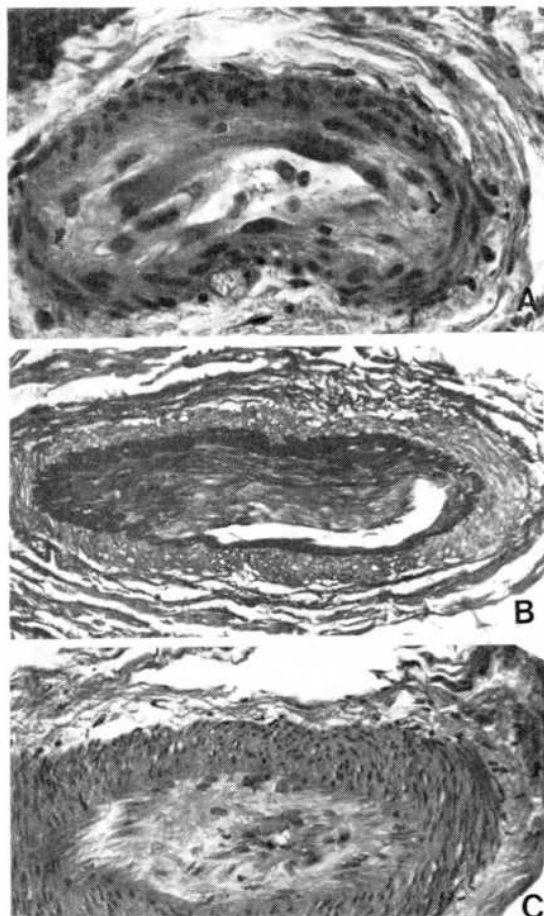


Fig. 4 Lesions in posterior ciliary arteries 6 months to 4 years after exposures of at least 6000 rads. A: Concentric proliferation of intima in a small artery. Notice large and prominent endothelial cells. (Haematoxylin and eosin, $\times 300$). B: Eccentric myointimal proliferation in large artery with thickening and duplication of elastic membrane. Notice marked reduction in lumen. (Verhoeff elastic-Van Gieson, $\times 124$). C: Severe concentric myointimal proliferation which has reduced the lumen of this large artery to a minute central channel. (Haematoxylin and eosin, $\times 124$).

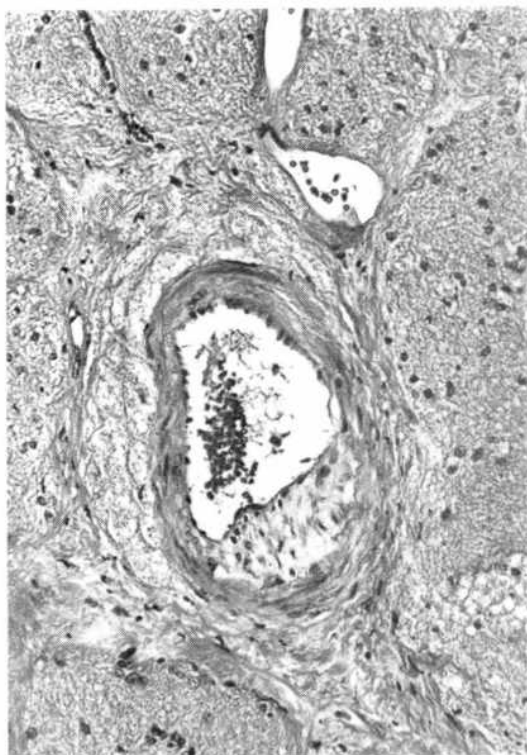


Fig. 5 Perpendicular section of optic nerve showing central retinal artery. There is an intimal plaque in the right lower quadrant. The vein (above) and the surrounding optic nerve are unremarkable in this field. (Haematoxylin and eosin, $\times 160$).

found that the ciliary arteries had developed significant alterations only a few months after standard therapeutic doses of radiation. Varying degrees of myointimal proliferation were found in most of the eyes that had been irradiated and none of the eyes that had not been irradiated. Conventionally it has been thought that the most radiosensitive ocular vessels are those of the retina.⁹ Our findings indicate the importance of damage to nonretinal as well as retinal vessels. Although histology alone is not a reliable indicator of blood flow, the severity of some of these changes raises the question of possible functional embarrassment of the posterior ciliary circulation, with ischaemia of the choroid and anterior optic nerve.

Previous histology of radiation-induced retinal vascular changes has shown thickening, hyalinisation, and occlusion.⁶ Retinal vascular changes observed with the aid of fluorescein angiography include capillary closure, vessel leakage, microaneurysms, and telangiectasis.^{5,7} The histological findings of occluded vessels explain capillary closure,

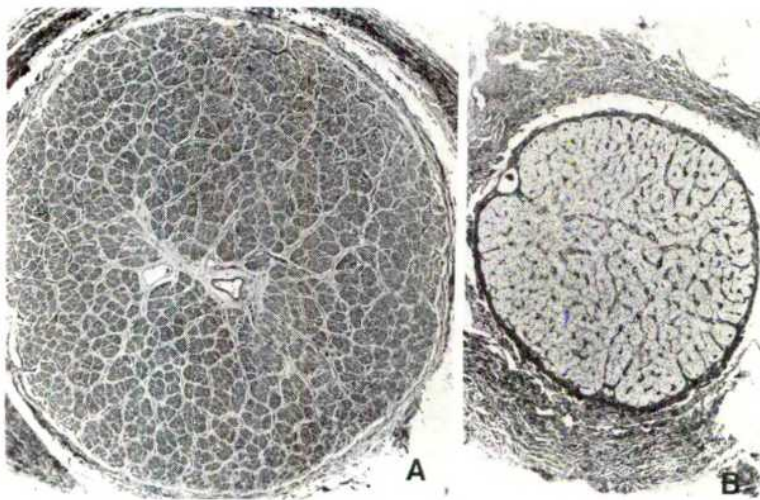


Fig. 6 Diffuse atrophy of optic nerve. A: Perpendicular section of normal optic nerve (child). The myelinated fascicles appear dark grey (bright blue in the preparation) and uniform. Compare with the adjacent photograph obtained at the same magnification and using the same stain.

B: Perpendicular section of optic nerve from eye resected 17 months after 6000 rads/20 fractions/35 days. Notice severe reduction in size and total, diffuse loss of myelin. (Luxol fast blue-PAS, $\times 17$).



Fig. 7 Segmental atrophy of optic nerve from a nonirradiated eye containing retinoblastoma. In this perpendicular section the nerve fibres (shown as fine dark dots at right, lower and left margins) are absent in a triangular segment (pale area in centre and upper left). (Bielschowsky silver impregnation, $\times 42$).

and the extravascular fibrin we observed is an indication of vascular leakage. Fibrin deposition should not be unexpected because it is a typical finding of delayed radiation injury in several tissues, including brain,⁸ pericardium,⁹ and subcutis.¹⁰ Central retinal artery occlusion is one of the possible complications of high-dose irradiation which has been clinically observed 1 to 2 years after treatment.³ The lesion of the central retinal artery is a myointimal proliferation which resembles the ciliary vessel changes we observed more than the retinal vessel changes.

Optic atrophy was a frequent feature in both irradiated and nonirradiated eyes. Although there was a tendency for irradiated eyes to show more diffuse atrophy than the nonirradiated eyes, an examination of a greater number of eyes would be necessary to prove this relationship. Radiation necrosis of the central nervous system is a well-known phenomenon and occurs more readily in white matter than grey matter.⁸ The damage is most probably mediated through vascular changes.¹¹ Optic atrophy has been observed after high doses of radiation, over 6800 rads,^{3,12} or after lower doses when combined with chemotherapy.^{13,14}

Our study has not demonstrated a clear time, dose, or age dependency of the ciliary artery lesions. Such an effect might be demonstrable either in a larger series of cases or in a prospective study having a wider range of radiation doses. Probably most of our patients have received doses above the threshold of arterial injury.

Radiation injury may take various forms and will vary from organ to organ, though it is usually consistent in a given organ. In the eye as in other tissues, with the notable exception of the liver and



Fig. 8 Segmental atrophy of optic nerve from tumour-containing, nonirradiated eyes. Normal axons are shown as fascicles of wavy black lines at the bottom. The axons are absent in the centre and scanty at the top. (Bielschowsky silver impregnation, $\times 115$).

intestine, there is a striking lack of lesions in ocular veins and sinusoids.¹⁰ Two features of the ocular changes are different from those found in other organs and deserve a comment: the irregular thickening of the retinal arterioles by a fine fibrillary material appears to be characteristic, since it is uncommon in most other tissues; unlike in many other organs and tissues in which fibrosis (i.e., collagen deposition) is typical of delayed radiation injury, we did not detect fibrosis of the choroid or sclera, even in the presence of severe narrowing of ciliary vessels.

We were surprised at the frequency of the vascular changes in the ciliary arteries and central retinal artery, occurring relatively soon after irradiation. If progressive, these changes could cause visual loss, either from central retinal artery occlusion, anterior ischaemic optic neuropathy, or choroidal ischaemia. Yet in a group of nonenucleated eyes in patients managed by the same method of radiotherapy and followed up for a mean of 11 years for visual function ischaemic changes were rare. Only 2 of 22

eyes had clinical optic nerve ischaemia, 1 macular ischaemia, and none central retinal artery occlusion.⁴ We do not know the reason for the discrepancy between the histopathological and clinical findings. One possible explanation is that radiation injury progresses rapidly for a limited time and then stabilises or progresses slowly.

Mrs Susan Lauber, Mrs Mia Hinze, and Mrs Irma Stadlbauer prepared the histological sections. Mr Jeff Shyshka prepared the photomicrographs.

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Fluorescein angiography in toxæmia of pregnancy

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SUMMARY The clinical and fluorescein angiographic findings in 2 cases of retinal detachment occurring in toxæmia of pregnancy are presented. Both cases showed angiographic evidence of abnormal choroidal leakage of dye unassociated with signs of retinal angiospasm. Both cases also showed angiographic evidence of delayed filling of the choriocapillaris. We believe this finding has not previously been reported. These observations provide further clinical evidence that retinal detachment in toxæmia of pregnancy is secondary to choroidal damage.

Toxæmia of pregnancy is characterised by generalised oedema, proteinuria, and hypertension, and generally occurs in the third trimester of pregnancy. The pre-eclamptic state progresses to eclampsia if convulsions supervene. Spontaneous retinal detachment in toxæmia was first reported by Von Graefe in 1855.¹ Although retinal detachment is now a well recognised complication of toxæmia of pregnancy, it is very uncommon.^{2–6}

The pathogenesis of retinal detachment in toxæmia of pregnancy is not fully understood, and both the retina and the choroid have been implicated as the source of the subretinal fluid in this condition.^{7–12} Previous reports in the literature describing fluorescein angiographic findings have suggested that detachment is secondary either to choroidal vascular damage alone¹³ or possibly to both retinal and choroidal vascular damage.¹⁴

This report describes the clinical findings in 2 cases of retinal detachment occurring in toxæmia of pregnancy. Fluorescein angiography showed evidence of choroidal leakage of dye as well as delayed filling of the choriocapillaris. We believe the latter finding has not been reported in the literature. These observations lend support to the hypothesis that retinal detachment in toxæmia of pregnancy is secondary to choroidal vascular damage alone.

Case reports

CASE 1

A 20-year-old primigravid, Hispanic woman was admitted to hospital in labour with a placental

abruption at approximately 34 weeks gestation on 21 September 1976 with a 1-day history of decreased vision in the right eye. The past medical history was unremarkable.

Physical examination showed a blood pressure of 150/100 mmHg, 1+ oedema, and mild deep tendon hyperreflexia. No fetal heart tones were heard, and fetal death was confirmed by fetal monitor. Ocular examination showed a visual acuity of 6/60 (20/200) in the right eye and 6/6 (20/20) in the left eye. External examination was normal except for a 1+ afferent pupillary defect on the right. Biomicroscopic examination of both eyes was normal. Ophthalmoscopic examination showed a serous retinal detachment involving the posterior pole of

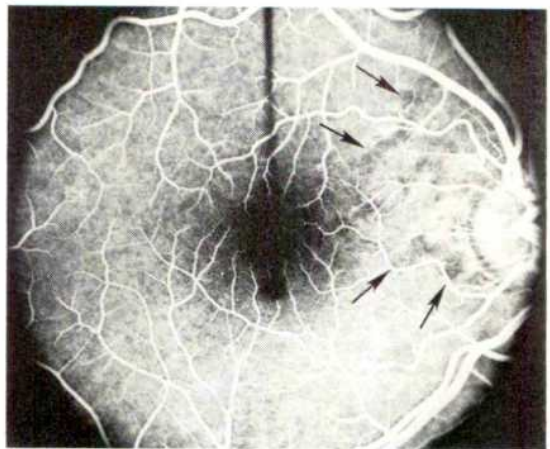


Fig. 1 Case 1. Fluorescein angiogram in early venous phase of right eye, seven days after delivery, showing delayed filling of choriocapillaris surrounding optic disc (arrows). Note normal retinal vasculature.

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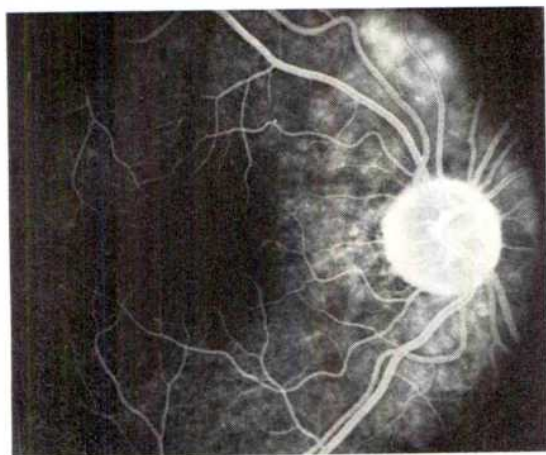


Fig. 2 Case 1. Fluorescein angiogram of right eye in late venous phase showing choroidal dye leakage surrounding optic disc.

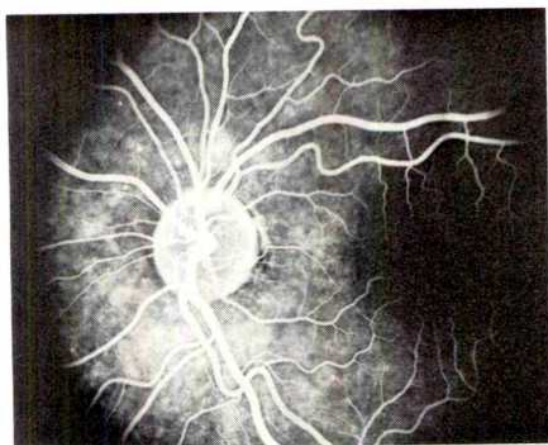


Fig. 3 Case 1. Fluorescein angiogram of left eye in late venous phase showing choroidal dye leakage surrounding optic disc.

the right eye. A peripapillary serous retinal detachment was present on the left without macular involvement. No retinal cotton-wool spots, haemorrhages, or arteriolar constriction were noted.

Urine analysis showed 1+ proteinuria. Other laboratory studies, including complete blood count, platelet count, fibrinogen levels, prothrombin time, and renal and liver function tests, were normal.

After a stillborn infant was delivered the vision in the right eye began to improve and the serous detachments gave signs of resolution. One week post partum fundus examination showed mild pigmentary disturbances in the right macula. A 1.5 disc diameter area of neurosensory retina was

raised inferotemporal to the right macula. Fluorescein angiography showed delayed filling of the choriocapillaris surrounding the optic disc in the right eye (Fig. 1). In the late venous phase there were numerous areas of dye leakage surrounding the optic disc bilaterally at the level of the choriocapillaris and pigment epithelium. These areas of hyperfluorescence enlarged and gradually coalesced (Figs. 2 and 3). There was mild staining of the subretinal fluid inferotemporal to the right fovea. No abnormalities of the retinal vasculature were noted.

The patient was last examined on 1 November 1976, and vision was 6/6 (20/20) in both eyes. The fundus examination was normal except for some minimal pigmentary changes in the right macula. Antihypertensive medications which were required during the patient's time in hospital were discontinued 12 days post partum, and the patient remained normotensive during the follow-up period.

CASE 2

A 36-year-old gravida-3, para-2, Hispanic woman was admitted to hospital at approximately 32 weeks gestation on 22 December 1975, with a 1-month history of progressive generalised oedema and shortness of breath and a 1-week history of bilateral decreased vision. She had had a fever and a swollen left leg for 2 days before admission.

Past medical history revealed that she had been treated intermittently for hypertension for several years and had 2 previous caesarean sections for unknown reasons, producing normal infants.

Physical examination showed an obese (270 lb (122 kg)) obtunded patient with anasarca. The blood pressure was 200/120 mmHg, pulse rate 140, temperature 102°F (38.9°C), and respiratory rate 40. Cellulitis of the lower left leg was present. Deep tendon reflexes showed unsustained clonus. On ocular examination she had a visual acuity of hand motion in each eye. External and biomicroscopic examination of each eye was normal. Ophthalmoscopic examination disclosed bilateral bullous serous retinal detachments. No retinal cotton-wool spots, haemorrhages, or vascular abnormalities were noted. Several small, whitish subretinal lesions were seen in the posterior pole of both eyes.

Abnormal laboratory studies were consistent with microangiopathic haemolytic anaemia¹⁵ and included: haemoglobin 8.6 g/dl, haematocrit 32%, white blood count $19 \times 10^9/l$, platelet count $40 \times 10^9/l$, and corrected reticulocyte count 4%. A peripheral smear showed a moderate number of fragmented red cells. Abnormal clotting function tests included a weakly positive protamine sulphate test and a slightly prolonged bleeding time. Fibrinogen level,

prothrombin time and partial thromboplastin time were normal. Bone marrow examination showed a hypercellular marrow with increased megakaryocytes. Urine analysis registered a 4+ proteinuria, 1+ bilirubin, and urobilinogen 8 Ehrlich units (normal up to 1). Abnormal or borderline low blood chemistries included: total bilirubin 2.1 mg/dl (35.9 μ mol/l) (normal 0.2–1.5 (3.4–25.6)), SGOT 170 Karmen units (normal 5–40), alkaline phosphatase 4.4 Bessey-Lowry units (normal 1–3), blood urea nitrogen 25 mg/dl (8.9 mmol/l) (normal 6–25 (2.1–8.9)), creatinine 1.7 mg/dl (150 μ mol/l) (normal 0.4–1.3 (35–115)), sodium 127 mEq (mmol) (normal 134–142), potassium 3.7 mEq (mmol) (normal 3.7–5.1), bicarbonate 18 mEq (mmol) (normal 21–29), chloride 96 mEq (mmol) (normal 96–105), uric acid 9.1 mg/dl (0.54 mmol/l) (normal 2.5–6.8 (0.15–0.4)), glucose 160 mg/dl (8.9 mmol/l) (normal 62–110 (3.4–6.1)), total protein 5.5 g/dl (55 g/l) (normal 6.5–8.3 (65–83)) and albumin 2.6 g/dl (26 g/l) (normal 3.9–5.0 (39–50)).

The patient was treated with intravenous magnesium sulphate, hydralazine, penicillin, and gentamicin. Ten platelet packs were required for stabilization.

Repeat caesarean section was performed, and a slightly macerated stillborn male infant was delivered from a fibroid uterus.

Postoperatively she received 4 units of whole blood; magnesium sulphate and antibiotics were continued, and a wound infection was opened and drained. Methyldopa and hydrochlorothiazide were begun on the third postoperative day. The platelet count and renal and liver function studies returned to

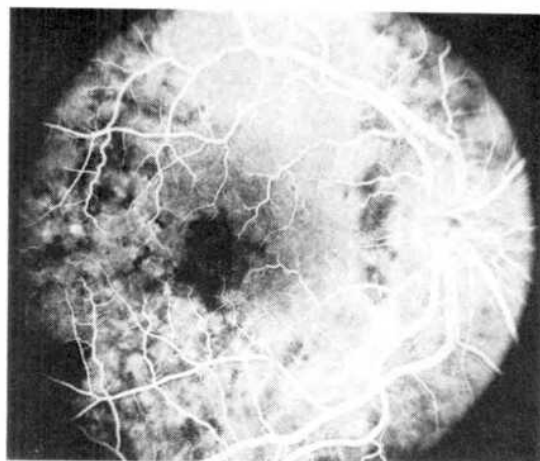


Fig. 5 Case 2. Fluorescein angiogram in early venous phase of right eye confirming delayed filling of choriocapillaris in posterior pole and showing early choroidal leakage. Note normal retinal vasculature.

normal, and the patient lost 60 lb (27 kg) by diuresis while in the hospital.

On 7 January 1976, 2 weeks post partum, the vision was 6/15 (20/50) in both eyes, and the detachments had largely resolved except for inferior subretinal fluid. Both maculae appeared to be slightly oedematous. Diffuse mild subretinal pigmentary disturbance was present in the posterior pole of both eyes. A few scattered whitish lesions were seen in the right eye underlying the macula. Fluorescein angiography of the retinal vasculature appeared normal. In the arteriovenous phase

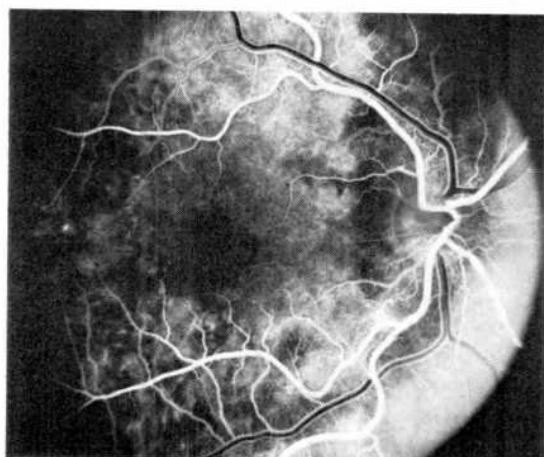


Fig. 4 Case 2. Fluorescein angiogram in arteriovenous phase of right eye, 14 days after delivery, showing delayed filling of choriocapillaris.



Fig. 6 Case 2. Fluorescein angiogram in late venous phase of left eye showing delaying filling of choriocapillaris and leakage of dye from choroidal vasculature.

delayed filling of the choriocapillaris persisted into the late phase of the angiogram (Fig. 4-6). Small dots of hyperfluorescence in both eyes were located at the level of the choriocapillaris and retinal pigment epithelium, and this staining increased in the late phase. Mild bilateral peripapillary staining was also present in the late phase of the angiogram.

The patient was discharged on 9 January 1976. She was last seen on 30 January 1976, at which time her vision was 6/12 (20/40) in the right eye and 6/9 (20/30) in the left. The fundi were normal except for some mild bilateral pigmentary disturbance in the macula. Her blood pressure remained poorly controlled on antihypertensive medication.

Discussion

Toxæmia of pregnancy usually occurs in the third trimester in primigravid women, who often have received inadequate prenatal care. Severe arteriolar spasm, evidenced by either segmental or generalised constriction, is the commonest finding in the fundus and has been reported in 70% of cases of toxæmia.¹⁶ Retinal haemorrhages, retinal oedema, and cotton-wool spots secondary to arteriolar damage may follow. Serous retinal detachments occur in the presence of severe pre-eclampsia or eclampsia, but only rarely. They may be seen in association with severe retinal vasospasm, haemorrhages, and exudates, but have also been reported in the absence of severe retinal arteriolar pathology.¹⁷

The incidence of serous retinal detachment in toxæmia of pregnancy varies, but all reports have emphasised the rarity of the condition. Fry³ noted a 1-2% incidence of retinal detachment in toxæmia and 10-4% in eclampsia. Hallum³ reported 6 cases in 300 pre-eclamptics. Mittelstrass and Wolfhagen⁴ reported 1 case in 873 eclamptics. Kronenberg⁵ reported 2 cases in 20 538 pregnancies, and Bosco⁶ reported 1 case in 18 524 pregnancies. We found only the 2 cases in this report in 62 832 deliveries at the Los Angeles County-University of Southern California Medical Center during a 5-year period (1974-78) in a patient population with approximately an 8% incidence of toxæmia. This observation confirms the previously reported low incidence of this condition. We suspect, however, that additional cases might have been discovered if ophthalmological examinations with indirect ophthalmoscopy had been performed on all toxæmic patients.

The pathogenetic mechanism for the production of serous retinal detachment in toxæmia of pregnancy is not fully understood. Clapp¹⁸ proposed that it was an extension of cerebral oedema. In a report on reversible retinal detachment in renal

failure Lapco *et al.*¹⁹ felt it was related to generalised oedema. Moore⁷ and Friedenwald⁸ believed the retinal detachments were secondary to retinal vascular damage, with Friedenwald presenting pathological evidence of acute necrosis of vessel walls.

In 1911 Verderame¹² demonstrated choroidal sclerosis in a post-mortem eye from a patient with toxæmic retinal detachment and was the first to postulate choroidal damage as the cause of detachment. Others have subsequently presented experimental, pathological, and clinical evidence that changes in the choriocapillaris and pigment epithelium are responsible.⁹⁻¹¹ Choroidal ischaemia and spontaneously reversible retinal detachments in 14 of 23 cats were produced by Collier⁹ by injecting a latex microsphere suspension retrograde into the vortex vein. Loss of the external layers of the retina and disruption of the normal pattern of the pigment epithelium were seen histologically. No occlusive effects were noted in the retinal vessels. Collier postulated that the mechanism of the serous detachment involved occlusion of the choriocapillaris, which resulted in increased choroidal hydrostatic pressure producing vasodilation, with subsequent transudation of fluid into the subretinal space. Stern and Ernest¹⁰ performed microsphere embolic occlusion of the posterior ciliary arteries supplying the choriocapillaris in rhesus monkeys. Small white patches of oedema in the external retina were caused by infarction of the retinal pigment epithelium and external retinal layers and corresponded to focal areas of fluorescein leakage on angiography. These white patches resembled the Elschnig spots seen in malignant hypertension, pre-eclampsia, and collagen vascular disease. Furthermore, retinal detachments developed in 2 monkeys made hypertensive with intravenous noradrenaline during the procedure. The pathological findings in serous retinal detachments in 3 patients with malignant hypertension and 1 with chronic glomerulonephritis were reported by Klein,¹¹ who established a direct relationship between ischaemic infarcts of the choriocapillaris and retinal separation. Thrombotic occlusion of the choriocapillaris with fibrinoid necrosis of the walls, the adjacent stroma, and the overlying pigment epithelium was demonstrated in 2 of the 4 necropsied cases. Another pre-eclamptic patient with serous retinal detachment recovered, but was left with small yellowish scars and central pigment deposits (Elschnig spots) thought to represent healed infarcts of the choriocapillaris. Cogan²⁰ noted that the ocular lesions of malignant hypertension, as described by Klein, had the same histological appearance as those in disseminated intravascular coagulation (DIC) and suggested systemic

coagulation as the pathogenetic mechanism. He reported the pathological findings in DIC, which included thrombotic occlusion of the choriocapillaris in the submacular region, choroidal haemorrhage, vacuolisation and disruption of the pigment epithelium with dispersion into the subretinal space, and serous detachment of the retina. Cogan postulated that the vulnerability of the submacular region in systemically induced hypercoagulability is presumably due to haemodynamic peculiarities of the circulation in this region.

Fluorescein angiographic studies of toxæmic patients with serous retinal detachment have been limited, partly because of fear of teratogenic effects on the fetus.²¹ Nevertheless, 2 detailed reports have appeared in the literature. Gitter and associates¹³ provided clinical evidence that the likely pathogenesis of the detachment is localised in the choroid. They reported a severe pre-eclamptic patient with bilateral serous retinal detachment without associated retinal vascular abnormalities. Fluorescein angiography performed prior to delivery showed a normal retinal vasculature, with the exception of a single constricted arteriole, and multiple areas of choroidal dye leakage with pooling of dye beneath the detachments. They suggested that dye leakage was due to transudation of fluid from the choroidal vessels into the subretinal space. Angiography performed 8 days post partum, when visual acuity had returned to normal, showed no leakage or pooling of dye. In contrast, Kenny and Cerasoli¹⁴ demonstrated clinically that detachment in toxæmia of pregnancy is secondary to changes in both the retinal and choroidal circulation. They performed colour fluorescein angiography in a patient with bilateral toxæmic retinal and choroidal detachments 48 hours post partum which showed abnormal retinal capillary filling as well as abnormalities in the pigment epithelial pattern. Their patient had marked involvement of the retinal vasculature, with narrowed arterioles, cotton-wool spots, and intraretinal haemorrhages.

The patients in the present report provide further evidence that retinal detachment can be secondary to choroidal damage alone. No evidence of retinal vasospasm, retinal haemorrhages, or cotton-wool spots was noted during the initial fundoscopic examination in either patient. Fluorescein angiography performed 7 days post partum in case 1 and 14 days post partum in case 2 revealed multiple areas of dye leakage which enlarged with time; they probably represented damaged areas of pigment epithelium which allowed dye to accumulate in the subretinal space. The fluorescein angiogram in case 1 showed delayed filling of the choriocapillaris in the peripapillary region of the right eye and the

posterior pole of both eyes in case 2. The angiographic finding of delayed filling of the choriocapillaris is a feature which has not been described previously in this condition and which occurs in occlusive choroidal vascular disorders such as hypertension, collagen vascular disease, diabetes, and blood dyscrasias.²² This differs from the physiologically normal 'patchy choroidal filling', in which the choroid shows early hypofluorescence but fills normally within 2-5 seconds. Presumably the nonperfusion of the choriocapillaris seen in these 2 cases resulted in ischaemia of the overlying pigment epithelium, with consequent late leakage of dye. No evidence of retinal vasospasm was noted in either angiogram. The possibility that retinal arteriolar abnormalities occurred acutely, but later disappeared, cannot be excluded, since the angiograms were done 7 and 14 days post partum.

Bill and Linder²³ demonstrated leakage of Evans blue dye out of uveal blood vessels of cats after sympathectomy during increase of the systemic blood pressure. In a study of the effects of systolic hypertension on rhesus monkey eyes after ocular sympathectomy Ernest²⁴ showed fluorescein leakage of dye from the uveal circulation in these animals that did not occur after ocular sympathectomy or systemic hypertension alone. Potts²⁵ has shown an increased blood flow and increased hydrostatic pressure through the macula, the vasculature of which is denser than in the retinal periphery. Although the exact mechanism remains unproved, these hydrodynamic factors, coupled with an alteration of sympathetic neural control in the hypertensive toxæmic patient, may play a role in causing choroidal vascular incompetency with resultant leakage and serous retinal detachment.

We thank Mr Bill Hart and Mr William Ludwick for taking the photographs and Ms Elva Barrera for secretarial assistance.

ADDENDUM. Since submitting this paper for publication 2 cases of choroidal nonperfusion in toxæmia of pregnancy have been reported.²⁶ Owing to predominantly abnormal choroidal vascular patterns the authors implicated choroidal vascular insufficiency as the primary basis for secondary retinal detachments seen in toxæmia of pregnancy.

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Fungal retinitis: a case of *Torulopsis glabrata* infection treated with miconazole

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SUMMARY Presumptive embolic chorioretinal *Torulopsis glabrata* infection is described in a patient who had received prolonged intravenous antibiotic therapy. The ocular findings are compared and contrasted with embolic lesions due to *Candida albicans*. The patient was treated for 6 weeks with intravenous miconazole. During this time there was shrinkage of the ocular lesions, some improvement in vision and abolition of fungaemia. Improvement in tests of immune function during treatment suggests that an early immunological deficit was secondary to the infection. Intravenous miconazole is a relatively nontoxic alternative to amphotericin and deserves further evaluation in the treatment of ocular mycosis.

Fungal infections occur in the immunologically compromised host and are a well recognised complication of intravenous antibiotic therapy¹⁻⁵ and intravenous drug addiction.⁶⁻⁸ Embolic ocular manifestations of systemic fungal infection generally present as chorioretinal lesions with subsequent anterior spread; *Candida albicans* is the organism most often implicated.^{9,10} *Torulopsis glabrata* may also cause fungaemia in similar circumstances, but retinal torulopsis has not been described. Amphotericin, the drug commonly used in the treatment of the ocular mycoses, may cause severe renal, hepatic, and bone marrow toxicity. Fluorocytosine is a less toxic alternative, but the organism may become rapidly resistant when it is prescribed alone.¹¹ Miconazole is a new drug being used in the treatment of systemic mycosis. It does not appear to have the serious adverse effects of amphotericin.

This paper describes a patient with chorioretinitis associated with *Torulopsis glabrata* fungaemia and the response of both ocular and systemic infection to intravenous miconazole.

Case report

A 31-year-old woman was referred to Sydney Hospital on 29 May 1979 with a 2-month history of blurred vision in the left eye, deteriorating further in the week prior to admission. In December 1978

she allegedly fell on a cup and deeply lacerated the left foot. Recurrent infection followed which necessitated prolonged intravenous antibiotic therapy. She was febrile on admission, and there was chronic inflammation with suppuration of the soft tissue of the dorsum of the foot. Regional lymph nodes were not enlarged.

Visual acuity in the right eye was 6/9 and funduscopy and fluorescein angiography were normal. Vision in the left eye was reduced to appreciation of hand movements in the peripheral field with no vision in the right upper quadrant. There was a minor vitreous haze. The optic disc was elevated, and there was a white circumscribed lesion surrounded by satellite bodies in the lower temporal quadrant (Fig. 1a). There was neovascularisation as well as traction of the retina, with gross distortion of the retinal vasculature and the macula.

Fluorescein angiography revealed a retinal mass immediately inferior to the macula surrounded by radiating capillaries, which fluoresced early. In the later phases of the angiogram there was gross leakage of dye from these capillaries, as well as from the temporal side of the disc (Fig. 2). These radiating vessels were interpreted as neovascularisation because they were anterior to the normal retinal capillaries in stereoscopic views.

The wound on the foot was explored and *Torulopsis glabrata* was cultured from debrided tissue. It was also grown on Sabouraud's medium from duplicate blood culture bottles. Cultures taken from

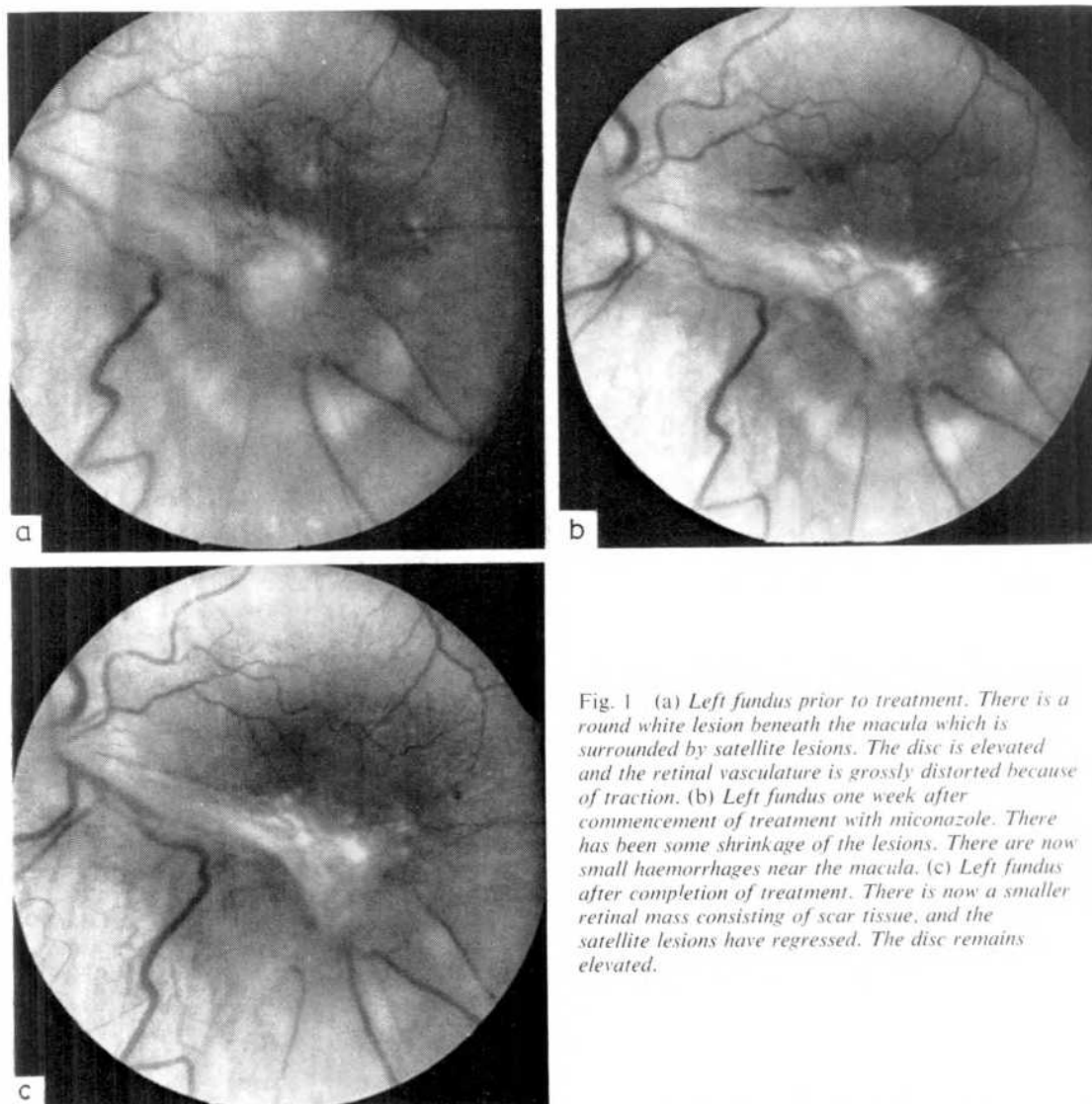


Fig. 1 (a) Left fundus prior to treatment. There is a round white lesion beneath the macula which is surrounded by satellite lesions. The disc is elevated and the retinal vasculature is grossly distorted because of traction. (b) Left fundus one week after commencement of treatment with miconazole. There has been some shrinkage of the lesions. There are now small haemorrhages near the macula. (c) Left fundus after completion of treatment. There is now a smaller retinal mass consisting of scar tissue, and the satellite lesions have regressed. The disc remains elevated.

the vagina and throat swabs showed a light growth of *Candida albicans*. Antibodies to *Torulopsis glabrata* were present in a titre of 1:320 and to *Candida albicans* in a titre of 1:80. The haemoglobin was 11.7 g/dl and the leucocyte count $8 \times 10^9/l$. There was slight eosinophilia ($1.26 \times 10^9/l$) and lymphocytopenia ($0.980 \times 10^9/l$). The erythrocyte sedimentation rate was 35 mm/h. The glucose tolerance test and tests of renal and hepatic function were normal.

The patient was initially thought to have had atypical ocular candidiasis. The structural changes at the macula suggested that prognosis for vision was poor. It was decided to treat the patient with

miconazole because of the known toxicity of amphotericin. Pending results of culture, treatment was commenced with miconazole by daily infusion of 1000 mg in 5% dextrose in water over 2 hours. This therapy was continued when blood cultures showed the presence of *Torulopsis glabrata*. Following the determination of the minimum inhibitory concentration (MIC=0.5 mcg/ml) and minimum fungicidal concentration (MFC=20 mcg/ml) of miconazole for this organism the daily dose was increased to 2400 mg as twice daily infusions over 1–2 hours delivered via a Raimondi catheter, which remained in place throughout the 6 weeks of therapy. The catheter has distal unidirectional

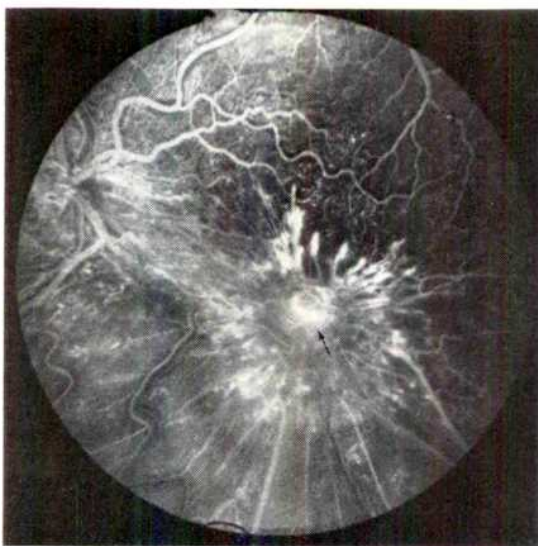


Fig. 2 Fluorescein angiogram of left fundus. The retinal mass is surrounded by radiating capillaries which fluoresced early. Stereoscopic views demonstrated capillaries anterior to the normal retinal vasculature. The pattern of fluorescence in the centre of the lesion was suggestive of chorioretinal anastomosis (see arrow).

valves, and is relatively resistant to thrombosis and infection. It was inserted because of poor venous access, despite reservations regarding the risks of prolonged central venous lines.¹²

One week after commencement of therapy small vertical haemorrhages were noted above the main lesion in the region of the macula (Fig. 1b). During the 6 weeks of treatment vision improved to 6/60, the vitreous cleared completely, and the satellite lesions regressed. The main embolic lesion also decreased in size significantly. Since discharge from hospital on 21 July 1979 the appearance of this scarred lesion (Fig. 1c) has remained static. Elevation of the disc due to traction has persisted. During treatment a pruritic rash developed which was treated with antihistamines. Blood cultures on 5 separate occasions, the latest on 8 October 1979, during and after completion of treatment have been consistently negative.

Immune function tests before treatment showed depressed cell-mediated immunity. T cell numbers (E rosette formation), as identified by their ability to bind sheep erythrocytes to their surfaces, were reduced to 34% of the total lymphocytes. B cell numbers were relatively increased to 58%. With treatment E rosette formation increased to 65% and B cells decreased to 31%. Antigenic skin tests for cell-mediated response using saline, candida and purified protein derivative (PPD) were all

negative on 1 June 1979, but a 4.0 mm area of induration to streptokinase-streptodornase (SKSD) developed. These tests improved with antifungal treatment to 6.0 mm induration with PPD and 20.0 mm to SKSD. There was persistent anergy to candida. The response of the patient's T lymphocytes to phytohaemagglutinin (PHA) was abnormally low prior to treatment and returned to normal during treatment. No circulating immune complexes were detected by the ¹²⁵I Clq precipitation test. Immune globulins were not reduced.

The electrocardiogram was normal and echocardiography showed no evidence of valvular disease. Fasting serum triglycerides and serum cholesterol were respectively 2.37 mmol/l (normal less than 1.70 mmol/l) and 6.5 mmol/l (normal 3.9–6.7 mmol/l) initially and rose during treatment to 12.4 mmol/l and 22.12 mmol/l respectively. Two months after the completion of therapy these figures had fallen to 2.40 mmol/l and 6.3 mmol/l.

Discussion

The clinical findings of a white retinal mass, with surrounding satellite lesions, seen in the context of chronic intravenous antibiotic administration or drug addiction, are strongly suggestive of embolic ocular fungal infection. In the present case the patient gave a history of trauma and prolonged intravenous antibiotic therapy, but the possibility that drug addiction was also a factor has not been dismissed. She has subsequently presented to 2 other hospitals in Sydney and given totally different accounts of her symptoms, and a Munchausen syndrome appears likely.¹³

Candida albicans was grown from throat and vaginal swabs, but the subsequent confirmation of deep wound infection and fungaemia with *Torulopsis glabrata* make it highly probable that this organism was responsible for the retinal lesions. Vitreous aspiration and culture⁷ were not thought justified in view of only minor vitreous haze.

Embolic ocular candidiasis is characterised by fluffy white inner retinal lesions, which rapidly spread anteriorly to cause severe vitreous opacification, which in chronic cases may obscure the retinal changes.^{5,6} Fluorescein angiography may reveal progressive fluorescence of retinal lesions, or areas of early hypofluorescence in areas of choroiditis,^{4,7} but new vessel formation is not described.

The clinical features in our case were different. Retinal vascularity with neovascularisation was striking. Vitreous involvement was minor, even though the clinical history and neovascularisation were consistent with a disease process extending over months.

Torulopsis glabrata is a yeast-like fungus, which is a normal saprophyte in man.¹⁴ It is related to candida, but can be differentiated from it by colonial appearance, lack of true mycelial growth, and by fermentation reactions. It is an opportunistic pathogen in immunosuppressed patients, and may cause fungaemia,^{12,15,16} systemic disease,¹⁷⁻¹⁹ and wound infection,²⁰ including infection following keratoplasty.²¹ Anterior chamber infection with both *Aspergillus flavus* and *Torulopsis glabrata* in a drug addict has been described by Elliott *et al.*⁸

The response of the patient's fungaemia and retinitis to miconazole is important. Amphotericin, which is generally effective in treating ocular mycoses,^{2,3,21,22} has potentially serious adverse effects which can complicate the already difficult course of an illness in debilitated and immune suppressed patients. The absence of these side effects is a major advantage for miconazole.²³

Miconazole is an imidazole derivative with a broad spectrum of activity against Gram-positive cocci and most fungal diseases, including candidiasis, aspergillosis, histoplasmosis, and infections with torulopsis. In low doses it is fungistatic, and therefore treatment may need to be prolonged to ensure adequate eradication of the fungus. At very high doses it is fungicidal. It penetrates well into most infected tissues, including vitreous humour,²³ but penetration into the cerebrospinal fluid is poor. Minor side effects include pruritus, rash, chills, phlebitis, and gastrointestinal symptoms, but no major adverse reactions have been reported to date. A transitory increase in blood lipids may occur, as in the present case, because of the lipid solvent (polyethoxylated castor oil) present in the parenteral form of the drug.

Initial investigation of the immune status of this patient revealed marked abnormalities of the cell-mediated response, as indicated by reduced E rosette formation, anergy of skin tests to common recall antigens, and absent response to PHA. During treatment most of these tests returned to normal, indicating that the fungal infection was most probably the cause of the immunological abnormalities. These abnormalities may have been due in part to the development of suppressor cells against the immune response to the fungus.²⁴ A more subtle defect in the ability of the patient's immune system to respond to fungal infection may still exist.

It would appear that miconazole represents a potentially useful alternative to amphotericin in the treatment of ocular torulopsis.

Dr J. Pollard for permission to report this case, and Mr G. Congdon for the fundus photography.

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Pseudomonas endophthalmitis associated with scleral necrosis

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SUMMARY Three cases of pseudomonas endophthalmitis associated with scleral necrosis 3 to 10 years after pterygium excision and beta irradiation are described. The value of prophylactic repair of radiation-induced scleral necrosis and early aggressive management of pseudomonas endophthalmitis are emphasised.

Pterygium recurrence is frequent after simple excision alone, especially in hot dry climates.¹ Beta irradiation is the only treatment that considerably reduces the recurrence rate, and it is frequently used after excision of primary pterygia.² Complications of beta irradiation for this nonmalignant lesion have received little attention. Scleral necrosis from beta irradiation after pterygium excision was first described by Jones and Reese³ and subsequently by Cameron,^{4,5} Cappin,⁶ and Talbot.⁷ This complication may occur years after beta irradiation and leads to a chronically irritable eye.

Pseudomonas endophthalmitis in such eyes has been reported only once.⁴ This paper reports 3 cases seen over 1 year and emphasises the importance of surgical repair of radiation-induced scleral ulceration.

Case reports

CASE 1

A 56-year-old European man had bilateral nasal pterygia excised leaving bare sclera in 1968. A total dose of 4000 rads of beta irradiation was applied to each eye over 2 weeks in 3 doses beginning on the 4th postoperative day. An oval strontium-90 applicator with an emission rate of 870 rads min⁻¹ and an active area of 18×13 mm was used.

The patient was asymptomatic until 1978, when the left eye became red and painful 3 days after it had been hit by a block of wood. On admission the visual acuity was counting fingers. The eye was hyperaemic with a copious mucopurulent discharge. A large necrotic scleral ulcer 6 mm in diameter

with a greenish base was present (Fig. 1) together with a large corneal infiltrate, a fibrinous iridocyclitis, a 1 mm hypopyon, and vitreous condensation. A heavy growth of *Pseudomonas aeruginosa* was cultured from the ulcer base, and diminishing numbers could be isolated until 21 days after admission. All were pyocin type UT/a.

Hourly gentamicin drops and intramuscular tobramycin (120 mg 8 hourly) were given for 3 days, but the eye deteriorated. Therefore treatment was changed to intravenous ticarcillin via a superior vena cava catheter (4 g in 20 ml normal saline infused over 10 minutes every 4 hours, that is, 24 g/day or 300 mg/kg/day) for 6 weeks together with oral probenecid 2 g daily. Tobramycin was given by subconjunctival injection (10 mg daily) for 2 weeks by continuous infusion into the upper fornix (320 mg l⁻¹ normal saline at 0.3 ml min⁻¹) for the second 2 weeks and then by oculum tobramycin



Fig. 1 Case 1: left eye, large necrotic scleral ulcer with endophthalmitis 10 years after pterygium excision and beta irradiation.

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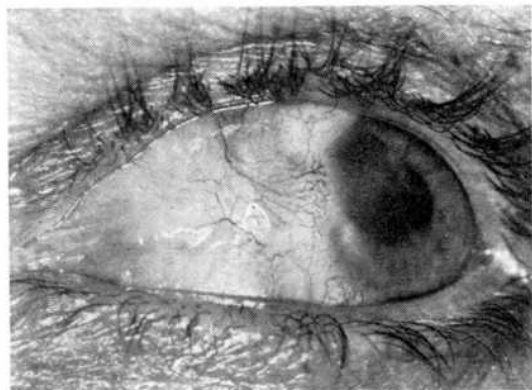


Fig. 2 Case 1: left eye, 1 year after a conjunctival flap.

0.3%, 6 times a day for 2 weeks. Six weeks after the patient's admission to hospital a conjunctival flap was placed over the ulcer, and antibiotics ceased 1 week later.

The right visual acuity was 6/5. An avascular thin cystic conjunctiva extended from 2 to 4 o'clock surrounded by tufts of episcleral vessels. The sub-jacent sclera was porcelain white. One year later the left visual acuity was 6/9. The sclera was well covered by conjunctiva. A superficial corneal opacity, posterior synechiae, moderate lens opacities, and membranous vitreous opacities were present (Fig. 2).

Early admission to hospital and intense and prolonged treatment were important factors in salvaging this eye. The ulcer site and size indicated that radiation-induced scleral pathology predisposed to the subsequent ulceration and infection.

CASE 2

A European man now aged 70 years had a left nasal pterygium excised leaving bare sclera in 1968. A total dose of 2800 rads of beta irradiation was given in 2 applications on the 6th and 11th days postoperatively. The source was the same as in case 1.

The eye was asymptomatic until 1978, when he presented to a rural hospital with a painful red eye. A history of trauma was denied. *Pseudomonas aeruginosa* was cultured from a conjunctival swab, and as the eye deteriorated he was transferred 1 week later. On examination there was a severe hyperaemia and a purulent discharge. Medially a large necrotic ulcer extended 2 mm on to cornea and 4 mm on to sclera. A corneal infiltrate adjacent to the ulcer and a 2 mm hypopyon were present. *Pseudomonas* was again cultured from conjunctival swabs. Despite gentamicin topically every hour and

intramuscularly (180 mg/day) and carbenicillin intravenously (30 g/day) the eye deteriorated, with extension of the scleral necrosis. The eye was eviscerated 3 weeks after the infection began.

The site and appearance of the ulceration indicated that radiation-induced necrosis predisposed the eye to *pseudomonas endophthalmitis*. The delay in starting treatment contributed to loss of the eye.

CASE 3

A 57-year-old Aboriginal woman had bilateral nasal pterygia excised leaving bare sclera in 1976. A total dose of 2400 rads of beta irradiation was applied over 2 weeks in 3 doses beginning on the day of operation. The applicator and dose rate were similar to that described above.

In September 1978 she presented with a 2-week history of a red painful photophobic eye. The visual acuity was right 6/12 and left 6/36. The reduced vision was due to lens opacities. Scleral necrosis was present medially in each eye, 2 mm from the limbus and 2 mm in diameter. The ulceration was almost full thickness with a grey-brown base composed of a thin layer of scleral fibres. The left eye was hyperaemic, with an iridocyclitis and corneal oedema. No organisms were cultured from conjunctival swabs. The eye settled with topical treatment, and 3 weeks later the left ulcer was closed with a scleral graft and conjunctival flap.

In June 1979 the patient was readmitted with a 1-week history of a right conjunctivitis progressing despite topical chloramphenicol and systemic amoxycillin. There was no history of trauma. The right eye had light perception only, gross periorbital oedema, marked conjunctival hyperaemia, corneal oedema, and a 360° peripheral ring hypopyon. The scleral ulceration was unchanged (Fig. 3).

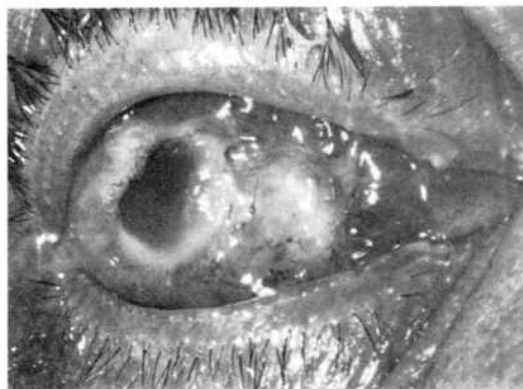


Fig. 3 Case 3: right eye, scleral ulceration with endophthalmitis 3 years after pterygium excision and beta irradiation.

Pseudomonas aeruginosa was repeatedly cultured from conjunctival swabs. Despite systemic gentamycin (120 mg daily) and carbenicillin (2 g daily) and topical gentamycin and chloramphenicol the condition of the eye worsened, and it was eviscerated 8 days after admission. The left eye had healed well (Fig. 4).

The bilateral nature of the deep scleral ulceration, the successful outcome of the operated eye, and the subsequent pseudomonas endophthalmitis and loss of the fellow eye serve to emphasise the importance of repairing scleral ulceration after beta irradiation.

Discussion

Pseudomonas aeruginosa is widely distributed in nature and can be found in water, soil, waste, and as a commensal of the intestinal tract and skin. The commonest ocular infection is a hypopyon corneal ulcer or abscess. Prior epithelial damage is often present. Rarely it causes postoperative endophthalmitis, lid infection, primary conjunctivitis, dacryocystitis, or orbital cellulitis.⁸ It is a classical opportunist, and infection particularly arises in patients predisposed by defective immunity or altered commensal flora by broad-spectrum antibiotics.

Radiation-induced scleral necrosis is an uncommon but an increasingly recognised complication of pterygium management. The above cases are from a group of over 40 patients seen recently in Western Australia with scleral ulceration. No longer can the sclera be considered resistant to radiation necrosis even after modest dosages of beta irradiation.

Infection in eyes with scleral disease has not been previously emphasised. No mention has been made of bacterial endophthalmitis as a complication of necrotising scleritis.^{9,10} However, pseudomonas endophthalmitis is a significant complication of beta irradiation-induced scleral ulceration. It occurred in one of 6 cases reported by Cameron.⁴ Talbot⁷ reported 13 cases of conjunctival and scleral ulceration of which two developed 'perforation, uveitis and blindness', but there is no mention of infection. Our cases indicate that pseudomonas may arise spontaneously in eyes with scleral ulceration even when this is only partial thickness. Such defects therefore should be repaired by a conjunctival flap or by a graft of sclera, cornea, fascia lata, or other tissue to prevent this devastating infection.

There is no ready explanation for the occurrence of pseudomonas infection in irradiation-induced scleral disease but apparently not in necrotising scleritis. Certainly scleral destruction is more extensive after scleritis than irradiation. Suppression of the immunological apparatus by x-irradiation is well known. However, experimentally Silverstein¹¹

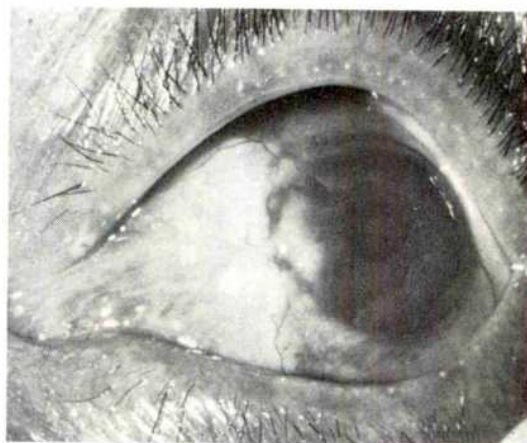


Fig. 4 Case 3: left eye, 9 months after a scleral graft and conjunctival flap.

has clearly shown that ocular irradiation has no effect on the activation of the immune system towards foreign antigens induced into the eye.

The large scleral ulcerations in cases 1 and 2 are atypical of beta irradiation-induced ulcers, which usually do not involve the cornea and are rarely as extensive. Most probably pseudomonas proteases extended the ulceration.

Salvage of one eye must be attributed to early, prolonged, and intensive antibiotic treatment. Persistence of pseudomonas organisms despite treatment and recrudescence of the infection after treatment is ended has been well described¹² and is an important factor in the management of pseudomonas infections. Prolonged treatment is therefore essential, and a continuous local delivery system is advocated.¹² This not only delivers the antibiotic continuously with minimal discomfort but also washes away pus, debris, and pseudomonas proteases. Antibiotic effectiveness is enhanced and further destruction of ocular tissue is minimised. The alternative—repeated subconjunctival injections—is extremely painful and irritative, so that the number of repeated injections is limited.

Synergism between ticarcillin and tobramycin has been demonstrated in vitro and in vivo.¹³ Adequate aqueous levels of tobramycin occur with subconjunctival and topical use.¹⁴ Ticarcillin is more effective than carbenicillin against pseudomonas.¹⁵ When pseudomonas organisms resistant to gentamicin or carbenicillin are present, or when the clinical response is inadequate, the combination of ticarcillin and tobramycin should be used.

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Post kala azar uveitis

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SUMMARY Three patients who developed bilateral anterior uveitis at the end of, or soon after, the apparently successful treatment of visceral leishmaniasis are described. The uveitis gave rise to secondary glaucoma in 2 of the patients, and in the third patient the eye lesions were associated with an episode of post kala azar dermal leishmaniasis.

Ocular complications of kala azar are uncommon.¹⁻⁵ Little distinction is sometimes made between the various species and clinical forms of human leishmaniasis. Actual case reports are very rare. In a paper that now seems to be available only as an abstract,⁶ 2 patients with iritis, one of whom also had retinal haemorrhages, and a third patient with papillitis are described. Recupero⁷ reviewed previous reports and described retinal haemorrhages in 6 children with kala azar. Superficial haemorrhages and cytooid bodies were seen in the retinae of a patient with kala azar probably acquired in Spain.⁸ McKie Reid¹ mentions in addition a central retinal vein thrombosis, a keratitis, and a chronic iritis. In all these the eye lesions have been a presenting feature of the kala azar. They regressed, together with the systemic illness, on treatment with pentavalent antimony.

Somerset³ states that involvement of the eye in post kala azar dermal leishmaniasis is exceedingly rare, but notes that there may be signs of chronic iritis.

Three patients seen at the Kenyatta National Hospital, Nairobi, during the last 8 years have developed anterior uveitis as a late complication of kala azar.

Case reports

CASE 1

A 37-year-old male Mkamba living in the area of Makueni, the centre of a recently^{9,10} noted epidemic of kala azar, first became ill in 1976. Kala azar was diagnosed in 1977, and he was treated with 60

injections of Pentostam (sodium stibogluconate) at an up-country hospital. Although he felt better, the spleen, of which he had been very much aware, did not recede completely. In 1978 the spleen enlarged again and he was treated at another up-country hospital with a further 60 injections of Pentostam. The spleen disappeared. A few days after discharge from that hospital he noted pain in both eyes together with deteriorating vision. He was referred to this hospital 3 months after the onset of the eye symptoms.

On examination visual acuity was restricted to the ability to count fingers at 1 metre (RE) and to detect hand movements at 30 cm. (LE). Refraction was +1 dioptre in both eyes. The conjunctivae appeared red with marked ciliary injection, the lower thirds of the corneal epithelia were oedematous, and numerous pigmented precipitates were seen in the lower thirds of the corneal endothelia. The anterior chambers contained a moderate number of tiny cells moving in the caloric stream, and a moderate flare was noted. Gonioscopy revealed circular peripheral anterior synechiae bilaterally. In both eyes the lens, posterior vitreous, retina, and posterior uvea were free from inflammation, but oedema of the macula and early glaucomatous cupping of the discs were noted. The intraocular pressures measured 52 mmHg (RE) and 42 mmHg (LE) with Goldmann's applanation tonometer.

On general examination the patient appeared to be in good health. The body temperature was normal, he was not anaemic, and his liver and spleen were not palpable. A few small hypopigmented macules on the forehead (Fig. 1) had been observed to develop during the preceding weeks by the patient. The leishmanin skin test and the Mantoux test were both positive. Results of investigations

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included haemoglobin 17.2 g/dl, leucocytes $5.6 \times 10^9/l$ with a normal differential, a platelet count of $255 \times 10^9/l$, a serum albumin level of 35 g/l and a globulin level of 38 g/l. A bone marrow aspirate was examined but no parasites were seen. There was no sugar or protein in the urine, and the blood urea was 42 mg/100 ml (6.97 mmol/l). The USR (syphilitic screening test) and a leishmanial fluorescent antibody test were negative, though the serum for this latter test was collected 8 months after the apparent cure of the visceral leishmaniasis.

Maximal standard therapy, namely, acetazolamide, mannitol infusions, systemic and topical corticosteroids, and trabeculectomy, was given for 2 months with little if any benefit. The surgical relief of intraocular pressure was associated with intra- and preretinal haemorrhages and lasted only for some 3 weeks because of the persistent inflammation.

He was then treated with Pentostam, 6 ml daily by intramuscular injection for 30 days. Systemic and local corticosteroids and acetazolamide were continued. On 2 occasions cyclocryotherapy was used to control rising intraocular pressures, still around 40 mmHg in both eyes.

The uveitis steadily improved on this regimen, and 5 months after admission he was discharged on acetazolamide, 125 mg 4 times daily, and corticosteroid eyedrops. The intraocular pressures measured 20 mmHg (RE) and 14 mmHg (LE). Visual acuity with correction was 6/60 (RE) and 1/60 (LE). In both eyes the anterior chamber showed some flare, but no cells were seen. The marked cupping of both discs persisted.

CASE 2

This patient was a 49-year-old male Mkamba from northern Kitui, the area of a major epidemic of kala azar that began shortly after the second world war.¹¹ He was not seen by us, but his records came to light while we were reviewing the records of patients with kala azar seen at the Kenyatta National Hospital over the last few years. He became ill in October 1972 and was admitted to this hospital in March 1973. He complained of periodic fever, weight loss and a mass, the spleen, in the left hypochondrium. Leishman-Donovan (L-D) bodies were seen in a marrow aspirate. Pentostam, by intramuscular injection, was given for 2 10-day courses of 6 ml daily and for a third course of 10 ml daily for 14 days. Ova of *Schistoma mansoni* were found on stool examination, and hycanthone 75 mg by intramuscular injection was given on 2 occasions a week apart. He improved, and a repeat marrow aspirate was normal.

Five months later when seen in the outpatients

department he was generally well, no hepatosplenomegaly was noted, but he complained of poor vision. The findings were of a granulomatous uveitis with secondary glaucoma. Vision without correction was 6/60 (RE) and 6/36 (LE). Both eyes showed ciliary injection, oedema of the corneal epithelia, especially on the right, and large precipitates on the corneal endothelia.

The intraocular pressures were 46 mmHg (RE) and 34 mmHg (LE) as measured by Goldmann's applanation tonometer. Treatment with depot corticosteroids, steroid eye drops, and acetazolamide was apparently successful, as the subsequent notes make no reference to eye symptoms or signs.

Three years later he was admitted with an inoperable malignancy of the stomach. The liver and the spleen were not palpable. The patient was not seen again at this hospital.

CASE 3

This patient, a boy, developed kala azar at the age of 2 years when living on the wall of the northern part of the Kenyan Rift Valley near Kapenguria. He was seen, aged 5 years, by one of us (PHR) after repeated unsuccessful courses of Pentostam and pentamidine. Splenic smears showed enormous numbers of L-D bodies. He received 3 30-day courses of Pentostam and a 3-month course of amphotericin B combined with 5-fluorocytosine, with some clinical improvement, but L-D bodies persisted in the splenic aspirate. A few days after completing a further 30-day course of Pentostam he developed an illness typical of post kala azar dermal leishmaniasis, with fever, malaise, conjunctivitis and a diffuse maculopapular rash, initially resembling measles, but becoming nodular with lesions some 4 mm across. The rash was especially on the face but also on the trunk and arms. Nodules were seen on the sclera, but the fundi appeared normal. L-D bodies were demonstrated both in skin scrapings and stained sections of the skin lesions. Pentostam was restarted and the rash cleared quickly, having been present for 4 weeks. The general malaise worsened, and investigation of this revealed that he was uraemic (blood urea 230 mg/100 ml = 38 mmol/l). The Pentostam was stopped on the 15th day of this final course, and he slowly recovered. Ten weeks later, although he was parasitologically cured and in good general health, he continued to complain of poor vision. Ciliary injection was still present, and ophthalmological examination disclosed corneal oedema and nodular iritis, especially inferiorly, in both eyes. A diagnosis of anterior uveitis with nodular iritis was made, and treatment with hydrocortisone and atropine eye drops given.

The boy was discharged home. Follow-up was difficult, but so far as can be ascertained no further complications developed.

Discussion

Although the last decades of ophthalmological history have taught us to be careful in postulating an aetiological connection between uveitis and some general disease, it is probable that the time relationship of the onset of the uveitis to the kala azar in these 3 patients is more than coincidental.

The first patient developed eye symptoms a few days after completing a curative course of Pentostam. The date of onset of the uveitis in the second patient is less certain, but must have been at some time during the weeks following cure. In the third patient the uveitis was apparently a part of post kala azar dermal leishmaniasis. Thus unlike the 2 patients described by Salvati,⁶ the uveitis occurred at or shortly after the conclusion of the systemic illness, post kala azar uveitis.

A consideration of the pathogenesis of the uveitis must be speculative, but an association with post kala azar dermal leishmaniasis seems likely. In the third patient the uveitis and the post kala azar dermal leishmaniasis appeared to be integral. In the first patient the rash on the forehead was in keeping with the East African form of post kala azar dermal leishmaniasis,¹²⁻¹⁶ though it should be noted that depigmentation of the lashes and/or a patchy depigmentation of the skin in association with chronic uveitis, such as in sympathetic ophthalmitis and in the Vogt-Koyanagi syndrome, is an observation of considerable age.¹⁸

The East African form of post kala azar dermal leishmaniasis occurs at the end of successful treatment or during the ensuing months. It is possible, though more difficult than in the Indian form,^{17, 18} to demonstrate parasites in the skin. The demonstration of these parasites suggests that the apparent parasitological cure of kala azar is relative rather than absolute. Post kala azar dermal leishmaniasis may be the outward sign of an immunological change, from the parasite-tolerant anergic state of kala azar to a parasite-intolerant state, manifest initially by much cellular reaction in the neighbourhood of parasites or sensitised cells, and then by parasitological cure or at least by a massive reduction in the parasite population. *Leishmania donovani* might be well tolerated in the anterior uvea during the anergic phase, but at the time of 'cure' these same parasites might form the focus of a uveitis. Such tiny lesions as we have described might be insignificant in other tissues such as the skin, but

in the anterior uvea will be obvious and may cause glaucoma and blindness.

Treatment is uncertain. Although the improvement in the first patient seemed to date from the introduction of Pentostam, the uveitis of the second patient probably recovered without the use of Pentostam, and in the third patient the eye lesions persisted despite the response of the post kala azar dermal leishmaniasis to Pentostam. The mode of action of pentavalent antimonials in kala azar remains unknown. Both a direct leishmanicidal effect and stimulation of the reticuloendothelial system seem improbable,¹⁹ and there are difficulties in accepting that chemotherapeutic activity depends on the reduction of pentavalent to trivalent antimony in the body.²⁰ If our speculations are correct, the inflammation could be expected to subside in due course without treatment, but perhaps not before irreparable damage had been done. Pentostam, or a similar pentavalent antimonial, and corticosteroids would seem to be sensible initial treatment, together with standard therapy for glaucoma should this develop.

We are most grateful to Dr P. E. C. Manson-Bahr for reviewing the first patient with us, to Dr D. S. Ridley for leishmanial serology on the same patient, to Dr A. D. M. Bryceson for supplies of leishmanial antigen, to our colleagues at the Kenyatta National Hospital for assistance with the care of these patients, to Dr P. S. V. Cox for referring case 3, to Dr W. Koinage Karuga, the Director of Medical Services, Kenya, for permission to publish, and to Marianne Egens de Sasso for secretarial assistance.

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Staphylococcus epidermidis endophthalmitis following intraocular lens implantation

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SUMMARY A 90-year-old man developed a hypopyon following cataract extraction with intraocular lens implantation. The hypopyon cleared with topical corticosteroid therapy but recurred whenever the corticosteroid therapy was reduced. At surgery for the removal of the intraocular lens an opaque anterior vitreous membrane was excised. Cultures of the anterior vitreous grew *Staphylococcus epidermidis*. The diagnosis was further confirmed by the histology of the anterior vitreous membrane, which showed Gram-positive cocci in the macrophages and polymorphonuclear leucocytes. This case shows that corticosteroids may completely mask an endophthalmitis from an organism of low virulence such as *Staphylococcus epidermidis*. Endophthalmitis from an organism of low virulence should be considered in any case of persistent postoperative inflammation.

Before 1973 the significance of culturing *Staphylococcus epidermidis* from the conjunctiva or aqueous humour in cases of endophthalmitis was disputed.¹ In 1973 Valenton *et al.*² reported 2 cases of *S. epidermidis* endophthalmitis where the diagnosis was confirmed by cytology and culture of aqueous removed by anterior chamber paracentesis. Forster and associates³ in 1976 reported a large series of cases with postoperative endophthalmitis and showed a high incidence of positive vitreous cultures for *S. epidermidis*. Five of the 6 eyes from this series which eventually attained useful visual acuity were cases of endophthalmitis caused by *S. epidermidis*. More recently Eichenbaum and associates⁴ reported 6 cases of *S. epidermidis* endophthalmitis in eyes following intraocular lens implantation.

We report herein a case of *Staphylococcus epidermidis* endophthalmitis occurring after intraocular lens implantation which masqueraded as a sterile endophthalmitis because it initially resolved with topical corticosteroid therapy.

Case report

A 90-year-old man underwent an uncomplicated right intracapsular lens extraction with the implantation of a 4-loop Binkhorst intraocular lens in

June 1978. The immediate postoperative period was uncomplicated. On the fifth postoperative day a mild inflammation was observed in the anterior chamber. This inflammation progressed to a 3 mm hypopyon by the seventh postoperative day. The patient was treated with a subconjunctival injection of gentamicin (20 mg) and topically applied dexamethasone 0.1% and gentamicin (3 mg/ml). The hypopyon was reduced within 24 hours and resolved 3 days after this treatment was initiated. The topical antibiotics were reduced while the topical dexamethasone was continued hourly because of the persistent cellular reaction in the anterior chamber. When the topical dexamethasone 0.1% was tapered to every 3 hours the hypopyon returned. The frequency of the topical corticosteroid was again increased to every hour, with complete resolution of the hypopyon within 48 hours. When the topical corticosteroid therapy was tapered to less than every hour, however, the hypopyon returned again, and again with hourly corticosteroid the hypopyon resolved completely within 48 hours.

The patient was seen in consultation in August 1978, 10 weeks postoperatively. At that time he was being treated with hourly topical dexamethasone 0.1%. Ocular examination revealed a visual acuity of light perception with good light projection OD and 20/80 OS. The intraocular pressure was 8 mmHg OD and 21 mmHg OS. There was a 2+ cellular reaction and heavy flare in the anterior chamber, but no hypopyon was present. A few scattered

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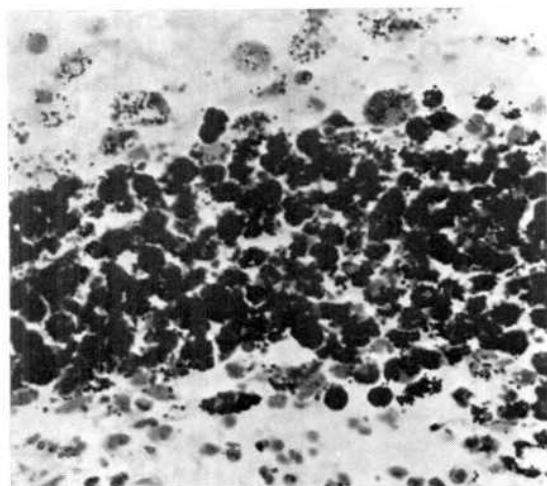


Fig. 1 Gram-stained smear of the anterior vitreous excised from the eye with endophthalmitis caused by *Staphylococcus epidermidis*. Numerous intracellular cocci are seen within the macrophages and polymorphonuclear leucocytes. ($\times 215$).

keratic precipitates were on the central corneal endothelium. A 4-loop Binkhorst intraocular lens was in place, and there were posterior synechiae to a partially organised vitreous membrane, which was located behind the intraocular lens. Ultrasonography revealed an apparently normal posterior pole.

The condition was diagnosed as a postoperative uveitis secondary either to the intraocular lens or to a low-grade endophthalmitis. Since the patient had no hypopyon on initial examination, the topical dexamethasone 0.1% was decreased to every 2 hours and topical gentamicin (3 mg/ml) was initiated. Three days later a hypopyon was present. On the following day, after an anterior chamber tap, the intraocular lens was removed, revealing a semi-opaque anterior vitreous. The anterior vitreous was partially excised and sent for histological and bacteriological analysis.

Trypticase broth cultures of the anterior chamber aspirate were sterile. However, cultures of the anterior vitreous grew *Staphylococcus epidermidis* (coagulase-negative, mannitol-negative) sensitive to penicillin, cephalothin, ampicillin, erythromycin, and neomycin. In addition, Gram and Giemsa stains of the anterior vitreous membrane revealed numerous macrophages and polymorphonuclear leucocytes with intracellular Gram-positive cocci (Fig. 1).

Postoperatively the patient was treated with oral dicloxacillin 500 mg 4 times per day, topical gentamicin (3 mg/ml) every 2 hours, topical Neo-

sporin (polymyxin B, neomycin, and gramicidin) every 2 hours, and topical dexamethasone 0.1% every 3 hours. The anterior chamber reaction cleared by the end of the first postoperative week, and the vitreous cleared one week later, allowing visualisation of a macular scar with overlying traction bands. Systemic and topical medications were gradually reduced, and the visual acuity returned to 20/200.

Discussion

Bacterial endophthalmitis usually presents 48 hours or more after cataract extraction, producing pain, decreased light perception and projection, anterior chamber reaction, vitreous reaction, and hypopyon.⁵ It must be differentiated from toxic iritis and sterile iritis, which may also cause a severe anterior chamber reaction in the first postoperative week. Toxic iritis presents in the first 24 hours after surgery and results from the introduction into the eye of disinfectants, soaps, or plastic products which have been sterilised with ethylene oxide. Sterile iritis may be observed at any time in the first postoperative week presenting with pain, anterior chamber reaction, vitreous reaction, and sometimes hypopyon. Fibrin and membranous opacification of the anterior hyaloid face commonly occurs in such cases. Sterile iritis is caused by trauma to the iris and ciliary body during the extraction of the lens. Both toxic iritis and sterile iritis respond rapidly to topical mydriatic and corticosteroid therapy, whereas a bacterial endophthalmitis will not do so. In 1976 Allen and Grove⁶ proposed that a reduction of postoperative inflammation within 24 hours after the initiation of topical corticosteroid and mydriatic treatment serves to differentiate an aseptic iritis from a bacterial endophthalmitis.

Early studies on the incidence of bacterial endophthalmitis following cataract extraction failed to demonstrate *Staphylococcus epidermidis* as a causative organism.⁵ Since 1973, however, there have been several reports of postoperative endophthalmitis caused by *S. epidermidis*,¹⁻⁴ and the pathogenicity of this organism is now accepted. In recent reports¹ *S. epidermidis* appears to be a significant cause of endophthalmitis following intraocular lens implantation.

Staphylococcus epidermidis is the commonest organism cultured from the conjunctival sac at the time of cataract extraction.⁶ The increased surgical manipulation associated with intraocular lens implantation may cause an increased intraocular inoculum of it during the operation. This may explain the relatively frequent occurrence of endoph-

thalmitis due to this organism after lens implantation.

The patient presented here is another case of *Staphylococcus epidermidis* endophthalmitis following intraocular lens implantation. As with many of Eichenbaum *et al.*'s⁴ cases, the onset of the postoperative inflammation in our patient did not begin until late in the first postoperative week. Similarly, our patient was initially misdiagnosed as a sterile¹ iritis.

The prompt resolution of the anterior chamber inflammation with topical corticosteroids was initially suggestive of a sterile inflammatory process. The persistence of the inflammation and the recurrence of the hypopyon whenever the corticosteroids were decreased ruled against a sterile process and suggested an endophthalmitis due to an organism of low virulence. Surgical removal of the intraocular lens revealed an organised anterior vitreous membrane. Cultures of the aqueous humour failed to yield any organism, though this may have been due to the topical antibiotic therapy. Cultures of the anterior vitreous, however, grew *Staphylococcus epidermidis*. The significance of this culture was further confirmed by cytology of the anterior vitreous membrane, which showed numerous macrophages and polymorphonuclear leucocytes with intracellular Gram-positive cocci. To our knowledge this is the first case report describing the histology of an anterior vitreous membrane caused by a *S. epidermidis* infection.

After the removal of the intraocular lens the ocular inflammation in this case responded rapidly to systemic antibiotic therapy. With the exception of 1 case reported by Forster³ all of the previous reported cases of *Staphylococcus epidermidis* endophthalmitis were treated with pars plana vitrectomy, with the injection of intravitreal gentamicin and cephaloridine. There have been no clinical series reporting the results of the treatment of endophthalmitis caused by this organism with topical and

systemic medication alone, though in a study of experimental *Staphylococcus epidermidis* endophthalmitis Cottingham and Forster⁷ showed this organism to be responsive to topical or intraocular antibiotics as well as to vitrectomy alone. The rapid response of our case to topical and systemic antibiotic therapy suggests that vitrectomy may not be needed in some of these cases.

This case re-emphasises the fact that with an endophthalmitis caused by an organism of low virulence the clinical signs can be masked by topical corticosteroid medication. Additionally, topical corticosteroid medication impairs the ocular immunological defence against the organism, resulting in unchecked growth of any bacterial population.

The possibility of a low-grade endophthalmitis due to *Staphylococcus epidermidis* or other organism of low virulence should be considered in any case of persistent postoperative inflammation, especially in the presence of corticosteroid treatment, and this clinical presentation should lead the surgeon to prompt culture of a vitreous aspirate.

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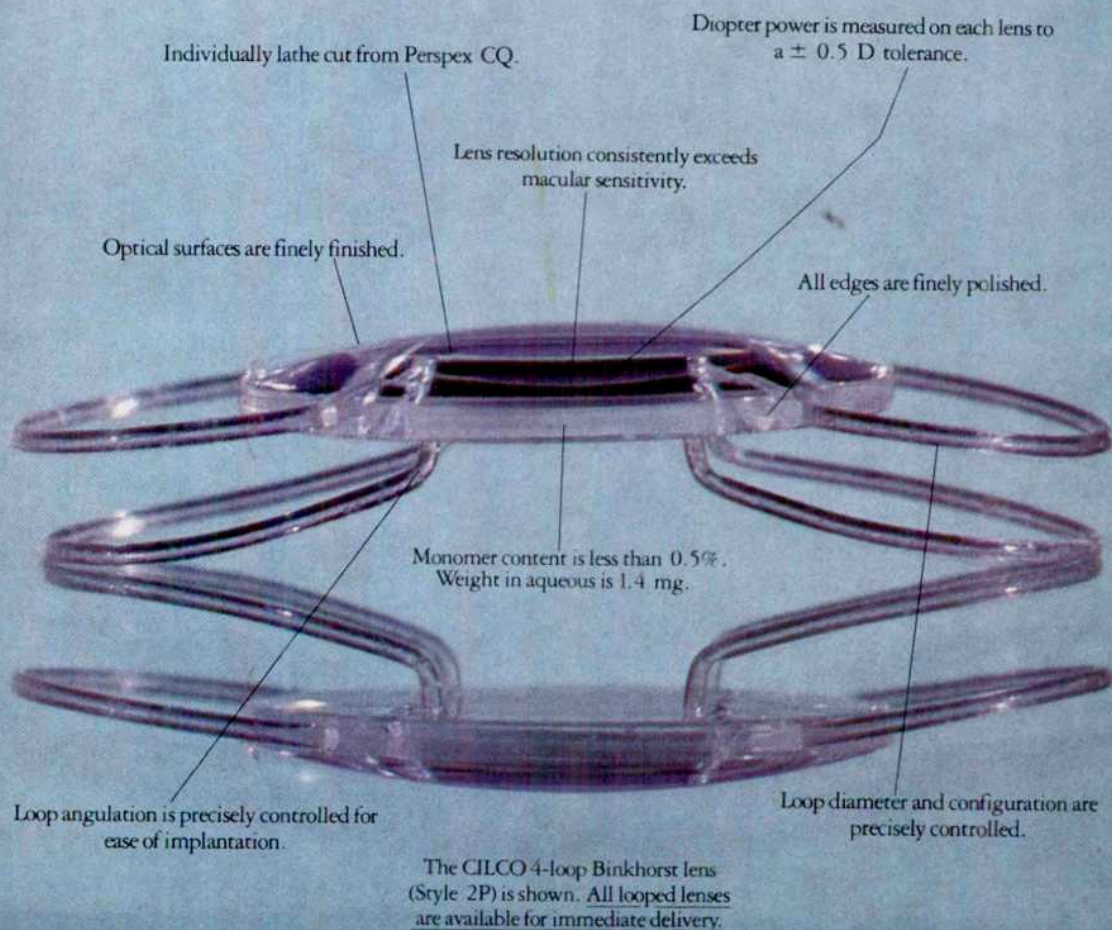
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Intraocular lens implantation by surgeons in training

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SUMMARY This paper is a retrospective study of 101 consecutive intraocular lens implantations with the Binkhorst 4 and 2-loop type lenses. The surgery represents a limited series of implant operations carried out by 10 surgeons of senior registrar grade on a programme of higher surgical training. When pre-existing adverse factors were excluded, the percentage of best visual results achieved was less than the best acuity levels reported by more experienced surgeons. The incidence of complications which could be related to surgical factors was found to be higher.

The 101 cases reported here are the results of intraocular lens implant operations carried out by 10 ophthalmic surgeons in training. The purpose of the study was to examine the visual results, identify the complications encountered, and to establish if possible the main factors which influenced the final visual outcome.

Materials and methods

With the exception of a small number of extracapsular lens extractions, which are discussed below, the majority of cataractous lenses were removed by a standard intracapsular cryoextraction technique. Ninety-six Binkhorst 4-loop lenses and 5 Binkhorst 2-loop lenses were implanted. Two surgeons carried out 58% of all the implant operations, and 2 other surgeons accounted for an additional 23% of the total. The remaining 6 surgeons carried out 20 cases in the total study. Surgery was carried out under general anaesthesia in all cases with the use of routine microsurgical techniques. The time of follow-up covered a period from 12 months up to a maximum of 6 years, and all except 4 eyes were available for follow-up evaluation. The corrected visual acuities were recorded in each case.

Results

After intraocular lens implantation 63% attained a visual acuity of 6/9 or better. An additional 9% attained an acuity of 6/12. The sum of these good visual results was 72% of the total. Three of these eyes had planned extracapsular lens extractions with

a Binkhorst 2-loop lens insertion, while the remainder all had intracapsular lens extractions and Binkhorst 4-loop lens implants.

In 25% of the total number of cases the visual outcome was considered poor, with a spectrum of visual results ranging from 6/18 to hand movements, and in 1 case there was finally no perception of light.

Discussion

When those cases which had a poor visual outcome for reasons unrelated to the surgical procedure are excluded, a good visual result following implant surgery was achieved in 79%. This compares with a 94% good visual result recorded by Roper-Hall¹ with a follow-up period of more than 2 years. Kratz² reports a 94% good visual outcome, but his follow-up time is significantly shorter. Dallas³ found that 67% of eyes after plain cataract extraction achieved a vision of 6/12 or better.

Though positive pressure ventilation was the preferred form of general anaesthesia, there was no evidence from examining this series of patients that spontaneous ventilation adversely influenced the visual outcome. A bulging forward of the iris plane or vitreous loss was uncommon with either form of anaesthesia, and operative hyphaemas or subsequent poor wound security could not be attributed to the prevailing form of anaesthesia.

No correlation was found between the visual results obtained and the pre-existence of poor general health, including chronic bronchitis, congestive cardiac failure, or maturity onset diabetes; patients with a diastolic blood pressure of 100 mmHg or over had an increased incidence of operative hyphaemas. Striate keratopathy persisting

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for 3 or more days after surgery was considered probably due to operative trauma. The main factor in this respect was thought to be endothelial touch by the implant or associated instrumentation at the time of implantation. A corneal section was used in 53 eyes, while a limbal incision beneath a conjunctival flap was used in 48 eyes; striate keratopathy was found in 47% of the corneal section eyes while it occurred in 51% of the limbal sections. Among the good visual results corneal and limbal sections were used in 57% and 43% respectively.

COMPLICATIONS

In 9% of the total number of cases complications were encountered which were considered not peculiar to intraocular lens implantation. These included pre-existing ocular pathology and some postoperative complications described below. One patient had pre-existing optic atrophy due to earlier radiation for an orbital neoplasm. An extracapsular lens aspiration in 1 case following childhood trauma, and an additional case with a congenital unioocular cataract, predictably resulted in 2 amblyopic eyes with consequently poor vision. One patient was found to have senile macular degeneration. In the postoperative period 2 eyes developed retinal detachments with poor long-term visual acuities. In 1 eye a central retinal vein occlusion led to poor vision. Another patient banged her eye 1 week after successful implant surgery and ruptured the globe with gross loss of intraocular contents. An additional eye was complicated by epithelialisation of the anterior chamber, and this eye was enucleated.

In a further 6% complications which could possibly be related to intraocular lens implantation were found. Four eyes with protracted uveitis developed secondary membrane formation. At surgery in three of these eyes an anterior vitrectomy following vitreous loss was necessary. On reviewing these eyes with uveitis there was a delay in instituting adequate topical treatment in the majority of cases.

Cystoid maculopathy was found by clinical examination in 2% to account for poor vision, which is less than the 12%¹ and 7%³ reported, but equal to the incidence following plain intracapsular cataract extractions.⁵ It is possible, however, that cystoid maculopathy could have been present in some other cases concurrently with corneal oedema

or membrane development and so evaded detection.

In the remaining 10% of cases endothelial decompensation occurred, and this complication was attributed predominantly to factors related to intraocular lens implantation. Half of this group initially enjoyed good vision, but after a period ranging from 11 months to 44 months their vision deteriorated from an acuity of 6/9–6/12 to 6/24—hand movements, due to corneal endothelial decompensation.

Two eyes with endothelial decompensation were additionally complicated by concurrent uveitis with membrane development and secondary glaucoma. Another eye with endothelial decompensation also developed glaucoma. In 3 of these eyes the lens implant was surgically removed. This course of action would seldom be advocated now.

In this series, the level of best visual acuity attained is lower than that of experienced surgeons. The incidence of complications will predictably be higher in the first 20 cases than in the next series.⁶ A poor visual outcome was found when an intraocular lens implantation followed a lens extraction complicated by vitreous loss. It should be noted that in half of the eyes in which endothelial decompensation was the cause of poor vision the onset of endothelial dysfunction was delayed for between 11 and 44 months after the original surgery. With a continually improving technique it is hoped that the incidence of endothelial decompensation will be greatly reduced.

I thank Mr W. Martin-Walker for encouraging me to review these patients.

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Glucose tolerance tests in 200 patients with senile cataract

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SUMMARY An account is given of asymptomatic diabetes mellitus. To determine the incidence in 200 patients with senile cataract 3 tests are described, namely, a modified standard glucose tolerance test, a provocative steroid glucose tolerance test, and a standard glucose tolerance test. Known diabetics and patients with a fasting blood glucose in excess of 5.5 mmol/l or glycosuria were excluded. Eighty-eight patients had an abnormal modified standard glucose tolerance test. Of these, 41 had an abnormal curve after a provocative steroid glucose tolerance test, and 30 had an abnormal curve after a standard glucose tolerance test. Forty-three of the 71 patients with abnormal curves had no glycosuria, although the blood glucose level exceeded an arbitrary renal threshold of 10 mmol/l. Asymptomatic diabetes was diagnosed in patients of all age groups. It is concluded that glucose intolerance is common in patients with senile cataract who show no glycosuria and have a normal fasting blood sugar on routine examination.

Diabetes mellitus presents not only in a clinical, overt, or symptomatic form but also in an asymptomatic (chemical) form, usually demonstrable only by blood and urine tests following the ingestion of glucose.^{1,2} Minor abnormalities in glucose metabolism may sometimes be discovered only by administering steroids to an individual prior to a standard glucose tolerance test.^{3,3}

The earlier definition of subclinical diabetes suggested by the World Health Organisation Committee were the synonyms 'asymptomatic', 'chemical', 'latent', and 'suspect diabetes'.⁴ Keen and Jarrett⁵ interpose between normal and pathological (or diabetic) values a category of 'impaired glucose tolerance' (IGT). They state that patients with sugar-free urine 1 hour after a standard glucose tolerance test are highly unlikely to have significant glucose intolerance. Furthermore they consider there is very little risk of the development of specific complications of diabetes in this group. Confusion may occur because of the different international criteria for the cut-off values in the diagnosis of diabetes mellitus based on an oral glucose tolerance test.⁶ In adolescence the asymptomatic form of diabetes is characterised by abnormal glucose tolerance tests and is classified as maturity onset type diabetes of young people (MODY), and in these cases the oral glucose tolerance test was

considered superior to the intravenous route in the screening of early abnormalities in carbohydrates metabolism.¹ No reports have appeared on the use of strictly defined parameters for the oral glucose screening of senile cataract patients to determine the incidence of asymptomatic diabetes.

Cataract is a known complication of diabetes mellitus. Patients with 'primary' cataract and senile cataract have been investigated by a standard glucose tolerance test, but an unreported number with a raised fasting blood sugar and glycosuria on preliminary investigations were included.^{7,8} Paufigue and Michand⁹ described 14 asymptomatic diabetic patients with cataracts but did not state whether the cataracts were senile nor which glucose tolerance test was used. Caird *et al.*¹⁰ found 3% of patients who had a senile cataract extraction were undiagnosed diabetics. In this paper we report the results in 200 patients with senile cataract investigated for asymptomatic diabetes by means of a modified standard glucose tolerance test and, if positive, a provocative steroid glucose tolerance test or a standard glucose tolerance test.

Patients and methods

There were 124 females and 76 males, their ages ranging from 55 to 86, who were diagnosed as senile cataract patients during a routine outpatient appointment over a period of 5 months at the Victoria Hospital, Burnley. One hundred and

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ninety-four patients had bilateral senile cortical lens opacities, and the binocular visual acuity with glasses was 6/18 or less. Six patients had had an extraction of a senile cataract, and the visual acuity in the unoperated eye was 3/60 or less. There was no further classification of the cataracts, and fundal changes were ignored because of the difficulty, or impossibility, of interpretation owing to impeded observation. Patients were selected for investigation solely on the diagnosis of senile cataract though known diabetics, and those showing glycosuria or a fasting blood sugar exceeding 5.5 mmol/l were excluded.

All patients had a diet containing 300 g of carbohydrate over a period of 3 days before the tests. Preliminary screening was by a modified standard glucose tolerance test. After a 12-hour fast a venous blood sugar was estimated by a modification of the Trinder AutoAnalyzer method; the patient drank 50 g of glucose and 1½ hours later another blood sugar was estimated. A second blood sugar of 5.9 mmol/l or less was considered normal. Patients with 6–8.9 mmol/l had a provocative steroid glucose tolerance test, and those with 9 mmol/l or more had a standard glucose tolerance test. The definition of the terminology was as described below:

(a) *Senile cataract.* A cataract was considered senile when congenital, complicated, traumatic, and known secondary causes were excluded.

(b) *Normal standard glucose tolerance test curve.* This curve showed a fasting blood sugar of 3.0–5.5 mmol/l. After half an hour, the 'peak', the blood sugar did not exceed 9 mmol/l, and 1 hour later returned to a fasting level.

(c) *Provocative steroid glucose tolerance test.* In addition to a standard glucose tolerance test the patient was prescribed a tablet of prednisolone 10 mg at 9 pm and at 7 am the next day, the latter tablet 2 hours before the first blood specimen.

(d) *Normal provocative steroid glucose tolerance curve.* This curve showed a fasting blood sugar of 3.0–5.5 mmol/l. The 'peak' was recorded at 1 hour and the blood sugar did not exceed 10.5 mmol/l. One hour later it returned to 7 mmol/l or less.

(e) The equivalent of 1 mmol/l in milligrams per cent was obtained by multiplying one SI unit by 18, and the renal threshold was an arbitrary 10 mmol/l. Fig. 1 illustrates a normal standard glucose tolerance test curve, a chemical diabetic curve, and a normal provocative steroid glucose tolerance curve.

Results

One hundred and twelve patients (56%) had a normal modified standard glucose tolerance test. Sixty-eight patients were females and 44 were males.

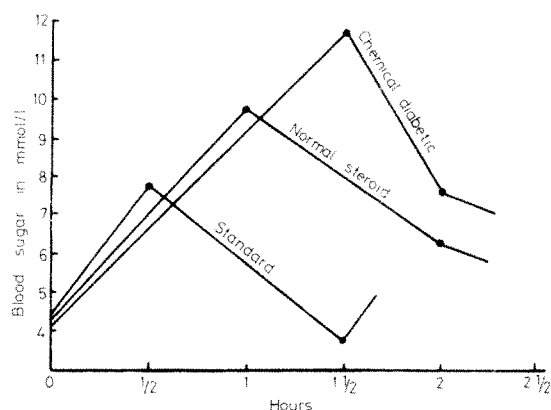


Fig. 1 Glucose tolerance curves.

Eighty-eight patients (44%) had an abnormal modified standard glucose tolerance test, of whom 56 were females and 32 were males.

Fifty-six patients (28%) had a provocative steroid glucose tolerance test; an abnormal curve was recorded in 41 patients, and they were classified as steroid sensitised chemical diabetics. Twenty-four patients were females and 17 were males. Twenty patients (10%) with an abnormal curve showed no glycosuria.

Thirty-two patients (16%) had a standard glucose tolerance test; an abnormal curve was recorded in 30 patients (15%) and they were classified as chemical diabetics. Eighteen patients were females and 12 were males. Twenty-three patients showed no glycosuria. In all patients with abnormal curves the arbitrary renal threshold was exceeded. Those with a disorder of carbohydrate metabolism were not confined to one age group but were randomly scattered.

The results and the relation to age groups are illustrated in Figs. 2, 3, and 4.

Discussion

There is a specific diabetic cataract, the 'snow-flake' cataract, but this is rare and occurs mainly in younger people.¹¹ In older people cataract has been found to be commoner in nondiabetics than in diabetics.^{12,13}

Other authorities have maintained a contrary viewpoint.^{14–16} If the asymptomatic diabetics with senile cataract are added to those cataract patients with symptomatic diabetes, the latter conclusion is fully substantiated. An abnormal carbohydrate metabolism may be associated with the aging process and could therefore be directly involved in the formation of senile cataracts. Of the 112 (56%)

patients with a normal modified standard glucose tolerance test 59 were aged 70 or over, and therefore a demonstrable disorder of carbohydrate metabolism was not responsible for their cataracts.

Van Selm⁸ stated that of the 186 'incipient' cataract patients investigated by a standard glucose tolerance test over 60% showed abnormal curves. This study revealed only 71 patients (35.5%) were asymptomatic diabetics, including those who had a positive steroid sensitised glucose tolerance test. The difference may be explained by his selection of patients. Their ages ranged from 18 to 92, and

patients with 'senile' cataracts were investigated only by a single test. It is pertinent to question whether 18-year-old patients can have senile cataracts, but the number of young patients was not quoted. Known diabetics were excluded, but not patients showing glycosuria or a raised fasting blood sugar. Private patients only were examined, and about two-thirds of those were female; therefore socio-economic and sex bias was a possibility. Similar criticisms apply to Langdon's paper. The cataracts were classified as 'primary', the ages of the 100 patients varied between 44 and 70, details of method were not included, and an undisclosed number of the 45 patients who 'showed an inability to digest the sugar meal' had an abnormal fasting blood sugar. Though patients with abnormal results were fewer than those recorded by Langdon⁷ and van Selm,⁸ the possibility of a senile cataract patient having an abnormality of carbohydrate metabolism should be considered regardless of age or body physique, as patients who have had a senile cataract extracted appear to be more likely to be diabetic.¹⁰

Fajans¹⁷ stated that the first signs of an impairment in carbohydrate metabolism are a shift to the right in the time of the peak and a delay in the return to normal serum values after a standard glucose tolerance test. The type of test after an abnormal modified standard glucose tolerance test was determined by values selected from a normal standard glucose tolerance test curve measured in milligrams per cent. 6 mmol/l was the nearest integer equivalent to the maximum normal fasting blood sugar of 110 mg per 100 ml. 9 mmol/l was the nearest integer equivalent to 160 mg per 100 ml, the maxi-

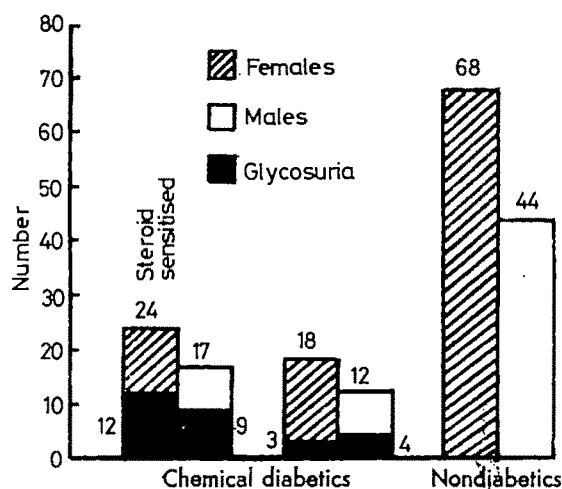


Fig. 2 Sex distribution of glucose tolerance tests' results and number of chemical diabetic patients with aglycosuria after a glucose tolerance test.

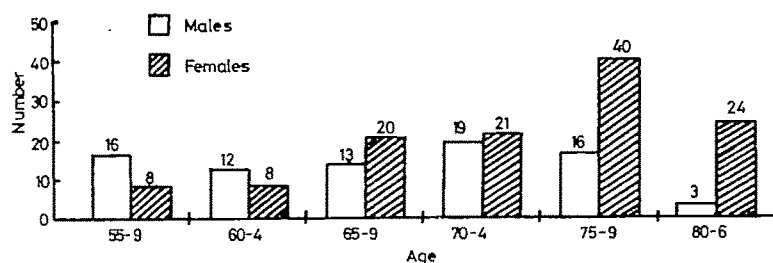
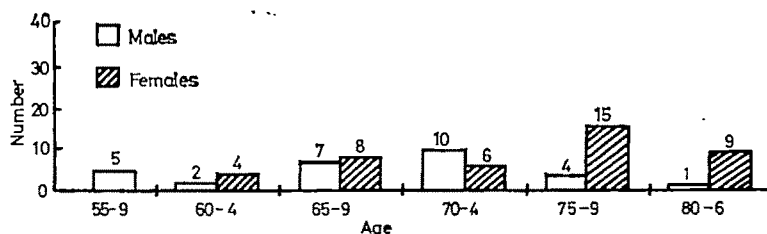


Fig. 3 Sex and age distribution of 200 patients with senile cataract.

Fig. 4 Sex and age distribution of 71 asymptomatic diabetics.



mum normal peak which should be recorded half an hour after the ingestion of glucose. Normal fasting blood glucose levels expressed in SI units are lower than those expressed in mg per 100 ml, and because of the fewer units to calculate SI units are less suitable for sensitive calibration.

Abnormal curves showed marked variation and the gross impairment of glucose metabolism recorded by some provocative steroid tests raised the query of the patient's possible response to a standard glucose tolerance test. The illustrated normal provocative steroid curve defines the maximum values, and many patients had lower serum glucose levels. No steroid sensitised patient had a raised fasting blood sugar with a normal provocative steroid curve. The older patients did not always have an exaggerated response to systemic steroids. The 15 negative provocative steroid tests were in patients ranging from 73 to 86 years of age. Testing for glycosuria after stressing the patient's glucose regulating mechanism by a meal rich in carbohydrate was not a reliable guide to the diagnosis of asymptomatic diabetes. Forty-three patients of the 71 chemical diabetics did not have glycosuria after drinking 50 g of glucose, but all the patients had a fasting blood sugar between 3.0 and 5.5 mmol/l, and during the test their blood sugar exceeded 10 mmol/l. Cataract patients can be effectively screened only by the simple modified standard glucose tolerance test. Its importance was shown by its leading to the diagnosis of chemical diabetes in 4 patients who had had one cataract extracted a few months prior to the test. At the time of operation urine analysis and a fasting blood sugar were normal. Clinical diabetes may occur in patients with asymptomatic glucose intolerance. They may be supervised by an ophthalmologist, preferably in collaboration with a physician who has a special interest in diabetes, though it must be stressed that future metabolic and clinical manifestations are not predictable. The effect of treatment by diet, insulin, or oral hypoglycaemics on cataract formation in an asymptomatic diabetic is unknown.

Caird *et al.*¹⁰ found that the development of cataract in the older diabetic was influenced by control of the diabetes. Consideration of the peculiar metabolism of the lens would support this finding.¹⁸⁻²⁰ The cataractous lens of the diabetic contains sorbitol, absent from non-diabetic lenses, and higher concentrations of glucose and fructose. The inverse correlation between inositol and glucose concentrations is not so marked in the diabetic lens as in the nondiabetic lens.²¹ Acid metabolites, common in diabetes, encourage the release of proteolytic enzymes which denature the lens fibres and lead to opacity. It is doubtful whether lactic

acid can be incriminated, because the concentration in the aqueous is identical in diabetic and nondiabetic patients (Reddy, personal communication). Hydration of the lens occurs because large protein molecules are broken down into smaller molecules, which exert an osmotic effect. The lens of an asymptomatic diabetic may be similarly affected.

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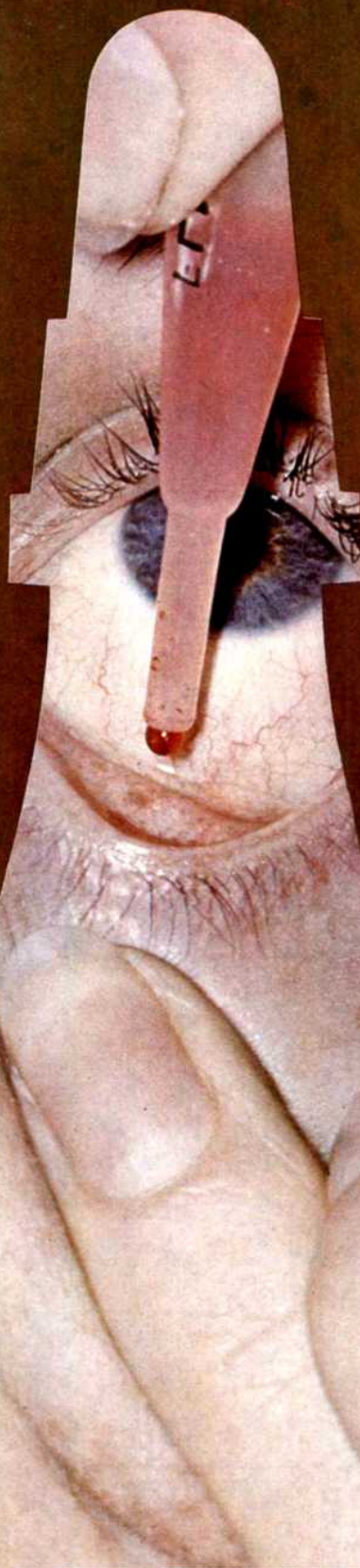
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Tear glucose levels in normal people and in diabetic patients

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SUMMARY Fifty normal people and 50 diabetic patients were studied by means of an enzymatic method for the glucose content in the blood, tears, and urine before and after the peroral glucose load. In normal subjects the fasting glucose levels in the tears averaged 3.6 mg/100 ml (0.2 mmol/l) and in the diabetic patients it averaged 16.6 mg/100 ml (0.92 mmol/l). As in blood and urine, tear glucose levels are significantly higher in diabetic patients than normal persons both at fasting and after the peroral glucose load test. The fasting tear glucose level did not appear to be a satisfactory index for classifying a person as a diabetic or normal. It was found that after the peroral glucose load test a tear glucose level at 11 mg/100 ml (0.61 mmol/l) resulted in only 4.6% of the diabetics being missed, while 5.8% of the normal persons were misclassified as diabetics.

It has been the practice to obtain blood or urine samples for glucose analysis to detect hyperglycaemia and diabetes mellitus. Collection of a blood sample is not always convenient and of a urine sample is messy. The difficulties are greater in mass surveys for detecting the prevalence of diabetes in a given population. Attention has therefore been drawn to the study of tear glucose to find out if it can be used as an alternative method for the detection of diabetes and hyperglycaemia. However, the data concerning its level in tears remain confusing and contradictory both as regards its normal level in tears and its relationship with hyperglycaemia.¹⁻⁴

The purpose of this project was to study the relationship between tear glucose and blood glucose in normal people and in diabetic patients before and after the peroral glucose load test. It was also intended to see whether any value of tear glucose could be used to separate diabetics and normal persons.

Patients and methods

Fifty cases of diabetes mellitus attending the Diabetic Clinic of Lok Nayak Jai Prakash Narain Hospital, New Delhi, with no detectable ocular changes were entered into this study. Their mean

age was 53.9 years (range 27 to 70 years). There were 32 males (mean age 47.3 years, range 27 to 66 years) and 18 females (mean age 56.7 years, range 40 to 70 years).

Fifty healthy people (mean age 41.7 years, range 22 to 75 years) who reported to the Outpatient Department of Guru Nanak Eye Centre, New Delhi, for refraction were entered as controls. There were 35 males (mean age 44.2 years, range 22 to 75 years) and 15 females (mean age 37.1 years, range 26 to 44 years).

Samples of blood, tears, and urine were collected after overnight fast and without the diabetic patients receiving any antidiabetic drugs. Tear specimens were collected by the method already described.⁵ All the samples were stored at -20°C and analysed on the same day. An oral load of 100 g of glucose was given to each subject. Further samples of blood, tears, and urine were collected 2 hours after the peroral glucose load test. The samples were analysed by the enzymatic method.⁶

Results

The mean, standard deviation, and coefficient of variation (CV) of the level of glucose in blood, tears, and urine in normal persons and in diabetic patients during fasting and after the glucose load are given in Table 1. It can be seen that there was considerable variation from one individual to another in fasting glucose level and the level after

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Table 1 *Blood, tear, and urine glucose in mg/100 ml in normal subjects and in diabetic patients*

	Blood					Tears					Urine				
	Fasting		Peroral load		Mean rise (%)	Fasting		Peroral load		Mean rise (%)	Fasting		Peroral load		Mean rise (%)
	Mean $\pm$ SD	CV (%)	Mean $\pm$ SD	CV (%)		Mean $\pm$ SD	CV (%)	Mean $\pm$ SD	CV (%)		Mean $\pm$ SD	CV (%)			
Diabetics	168.2 $\pm$ 61.8	36.7	280.1 $\pm$ 81.6	29.1	66.5	16.6 $\pm$ 9.4	56.6	43.1 $\pm$ 19.1	44.3	159.6	44.8 $\pm$ 49.1	109.5	138.6 $\pm$ 89.8	64.7	209.4
Normals	76.5 $\pm$ 10.3	13.4	107.6 $\pm$ 18.3	17.0	40.6	3.6 $\pm$ 2.6	72.2	6.0 $\pm$ 3.2	53.3	66.7	6.0 $\pm$ 3.7	61.6	14.5 $\pm$ 5.8	40.0	141.7

SI conversion: mmol/l = mg/100 ml $\times$ 0.0555.

the glucose load in blood, tears, and urine both in normals and diabetics. The mean fasting level of glucose in blood, tears, and urine in diabetics was significantly higher ($P < 0.001$) than in normal persons. There was no significant correlation between glucose content of blood and tears among normal persons and diabetics (normals: $r = 0.17$, for 48 DF $P \gg 0.10$; diabetics: $r = -0.03$, for 48 DF $P \gg 0.10$). A significant rise of glucose level after the glucose load was found in blood, tears, and urine both in normal persons and in diabetics. The mean percentage rise of glucose level in blood, tears, and urine after the glucose load was more in diabetics. The mean percentage rise in the glucose level in tears was more than the percentage rise in blood after the glucose load in diabetic subjects.

On the assumption of a normal distribution an estimate was made of the proportion of diabetics who would be wrongly classified if a particular glucose level in tears and in urine was considered to separate the 2 groups.

TEARS

Tables 2 and 3 show the percentage of subjects misclassified with different critical levels of fasting glucose and those after the glucose load. Whereas the fasting glucose level did not appear to be satisfactory for the purpose of classification into diabetics and normal persons, very good results were obtained when the glucose level after the glucose load are considered. For example, with the level of glucose at 11 mg/100 ml (0.61 mmol/l) only 4.6% of the diabetics and 5.8% of the normals would be wrongly classified (Table 3).

URINE

None of the glucose values in fasting samples were found to be satisfactory for the purpose of classification into diabetics and normal persons (Table 4). The percentage of diabetics misclassified as normal was too high for all the levels considered, namely, 10 to 17 mg/100 ml (0.56 to 0.94 mmol/l). When the values lower than 10 mg/100 ml (0.56 mmol/l) were

Table 2 *Misclassification with different critical levels (mg/100 ml) of fasting tear glucose level*

	Percentage misclassified at level						
	4	5	6	7	8	9	10
Diabetics	9.0	10.9	12.9	15.4	18.1	20.9	24.2
Normals	44.4	30.2	18.7	10.2	5.0	2.1	0.8

SI conversion: mmol/l = mg/100 ml $\times$ 0.0555.Table 3 *Misclassification with different critical levels (mg/100 ml) of tear glucose after peroral glucose load*

	Percentage misclassified at level							
	10	11	12	13	14	15	16	17
Diabetics	4.2	4.6	5.2	5.7	6.4	7.1	7.8	8.5
Normals	10.4	5.8	3.0	1.4	0.6	0.2	0.1	0.0

SI conversion: mmol/l = mg/100 ml $\times$ 0.0555.Table 4 *Misclassification with different critical level (mg/100 ml) of fasting urine glucose*

	Percentage misclassified at level							
	10	11	12	13	14	15	16	17
Diabetics	23.9	24.5	25.1	25.8	26.4	27.1	27.8	28.4
Normals	13.6	8.5	5.0	2.7	1.4	0.7	0.3	0.1

SI conversion: mmol/l = mg/100 ml $\times$ 0.0555.Table 5 *Misclassification with different critical levels (mg/100 ml) of urine glucose after peroral glucose load*

	Percentage misclassified at level							
	24	25	26	27	28	29	30	31
Diabetics	7.5	7.6	7.9	8.1	8.2	8.4	8.5	8.7
Normals	9.0	6.9	5.3	3.9	2.9	2.1	1.5	1.0

SI conversion: mmol/l = mg/100 ml $\times$ 0.0555.

considered, the percentage of normal persons misclassified as diabetic were unacceptably high. However, the glucose levels after the glucose load are more satisfactory (Table 5). For example, with

a critical value of 26 mg/100 ml (1.44 mmol/l) only 7.9% of the diabetics and 5.3% of the normals would be wrongly classified.

Discussion

Several workers have studied the glucose level in tears in normal subjects (Ridley¹—65 mg/100 ml (3.6 mmol/l), Borsellino⁷—27 mg/100 ml (1.5 mmol/l), Giardini and Roberts⁸—2.6 mg/100 ml (0.14 mmol/l) Gasset *et al.*³—4.1 mg/100 ml (0.23 mmol/l), and Motoji⁸—7.2 mg/100 ml (0.4 mmol/l)). In our study it averaged 3.6 mg/100 ml (0.2 mmol/l) in normal subjects.

Michail *et al.*⁹ first demonstrated in 1937 the rise of tear glucose during hyperglycaemia (alimentary and diabetic). Lewis and Stephens⁴ and Giardini¹⁰ studied the level of tear glucose in diabetic patients and found it to be often raised, though the increase bore no relationship to blood glucose. Gasset *et al.*³ and Motoji⁸ found a definite relationship of tear glucose and blood glucose and concluded that hyperglycaemia could be detected by measuring tear glucose level. However, in the present study, no significant correlation was found between the glucose level of blood and tears.

Gasset *et al.*³ measured changes in the tear glucose level following oral glucose load and found an increase in the tear glucose level in diabetic patients but no significant rise in the tear glucose level in normal subjects. Motoji⁸ also studied the glucose level in tears in normal subjects and in diabetics before and after peroral glucose load. He found that, while the glucose level in the tears tended to run parallel with the blood glucose level, the former tended to be higher for the same blood glucose level after the peroral glucose load. In our study the mean percentage rise in the level of tear glucose after the peroral glucose load was more than the mean percentage rise in the level of blood glucose both in normal persons and in diabetics, but it was found to be higher in the latter.

Since it was found that, after the glucose load,

tear glucose level at 11 mg/100 ml (0.61 mmol/l) was a reliable guide for classifying a person as diabetic, tear glucose levels in the postprandial phase or after giving oral glucose load can be used as a screening device for picking up diabetic cases. Subjects with values higher than 12 mg/100 ml (0.67 mmol/l) could be labelled as diabetics. Subjects with levels between 9 mg/100 ml (0.5 mmol/l) and 12 mg/100 ml (0.67 mmol/l) could be considered suspicious and subjected to detailed blood glucose analysis.

This finding can be taken advantage of in surveying the prevalence of diabetes in a population. Persons without diabetic symptoms would be less reluctant to give samples of tears than of blood. Thus a fairly accurate estimate of the prevalence of diabetics could be made with less resistance from the public.

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Fluid uptake in Schirmer papers and its relevance to their employment in tear collection for lysozyme tests

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SUMMARY An investigation was undertaken into the relationship between the wet length of a standard Schirmer paper and the fluid weight in the 5 mm tip after a 5-minute moistening period. Immediate weighing after moistening showed that it is unreliable to infer a particular fluid weight in the 5 mm tip from a known wet length, and it is concluded that such papers will lead to error in lysozyme tests. If the papers are inserted for a period within sealed envelopes, there is found to be a close relationship between wet length and fluid weight in the tip, the papers reaching a stable state at 5 hours. Soaked Schirmer papers were shown to give particularly inconsistent results.

Tear samples may be collected for lysozyme estimation by employment of filter paper discs^{1,2} or Schirmer papers.^{3,4} In these procedures it is necessary that the weight of each individual sample be determined unless the paper is known to take up a constant quantity of tears. A previous paper⁵ gave an account of the weight of tears collected by 6 mm filter paper discs, and the present work was undertaken to investigate fluid uptake in Schirmer papers.

Preliminary investigations

Preliminary work showed that there was rapid fluid loss by evaporation from moist filter paper samples, and it was necessary to understand and control this factor before further research could be undertaken. Serial weighings of 5 mm filter paper squares (Whatman no. 41) moistened with water revealed that the evaporation rate varied with relative humidity, but was independent of the weight of fluid in the paper. A series of moist filter paper squares was therefore weighed under differing conditions of relative humidity to compare the evaporation rate with the wet bulb depression of a wet and dry bulb thermometer placed beside the balance. Fifty-three tests were undertaken, each determining mean loss of moisture from two 5 mm filter paper squares weighed over a period of 10 minutes. Within the temperature range 12.8 to 26.7°C (55 to 80°F) a very close relationship was

demonstrated between the rate of evaporation and the wet bulb depression (correlation coefficient 0.97, $P < 0.001$). It was concluded, therefore, that a simple reading of wet bulb depression could replace measurement of evaporation rate. Determination of relative humidity was also unnecessary.

Subsequent experiment showed that the relationship between the length of Schirmer paper wetted and the fluid weight in the first 5 mm portion is altered by several factors. These factors were covering a section to reduce evaporation, whether one or both surfaces were freely exposed to the air, and the time interval between moistening and weighing even when correction had been made for evaporation loss. It was decided therefore to set up a model resembling the normal Schirmer procedure, in which a paper is placed over the lower lid and moistened by tears for a period of 5 minutes.

Material and methods

Standardised Schirmer papers 5 mm wide and 35 mm long (Whatman no. 41, Halberg and Berens) were taken, and the rounded end was cut off at the 5 mm notch and discarded, thus leaving a 30 mm long paper with square-cut end. The first 5 mm length of this shortened paper was placed on a nonabsorbent surface and lightly covered with a 5 mm wide strip of plastic adhesive tape, the remaining 25 mm being so placed that both surfaces were freely exposed. The temperature and wet bulb depression at the site were noted, and by means of a micropipette a 1% aqueous solution of fluorescein was intermittently applied to the edge of the covered

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end over a period of 5 minutes. The length of moistening, including the covered 5 mm, was then measured, the fluorescein colouration facilitating this reading, after which either of two procedures was followed. In the first the covered 5 mm end of paper was immediately cut off with a razor blade and the moisture content determined by weighing wet and then reweighing after drying at room temperature. In the second procedure the whole strip was immediately placed in the plastic envelope in which it is supplied, usually 2 strips per envelope, and this was sealed inside with petroleum based gum (Studio Gum) and outside with plastic adhesive tape. (Early trials showed that evaporation from the envelope was not entirely abolished by the tape alone.) After a chosen period of time the strip was removed from the envelope and the 5 mm tip was cut off and weighed wet and then dried, as in the first procedure. The weight of fluid in the 5 mm end of Schirmer paper was thus determined for a range of moist lengths and under different conditions of wet bulb depression, both on immediate weighing and after elapse of the following time intervals: $\frac{1}{2}$ hour, 1, 2, 3, 4, 5, 6, and 8 hours.

Results

IMMEDIATE WEIGHING

Trials were conducted under 4 different conditions of wet bulb depression. Eleven papers were tested at 5.8°C depression, and 12 each at 6.9 and 7.5°C , but in none of these series was a statistically significant correlation found between wet length of paper and fluid weight in the 5 mm tip. The tip fluid weight ranged from 1.5 to 3.1 mg. At a depression of 5.3°C the correlation between the 2 variables was found to be significant in a trial of 12 papers, and therefore tests were extended to a total of 37. These confirmed a relationship between wet length and tip fluid weight, but there was still a very wide spread of readings (correlation coefficient 0.62, $P < 0.001$), and the tip fluid weight ranged from 0.5 to 4.6 mg.

DELAYED WEIGHING AFTER SEALING IN ENVELOPES

Twenty-one trials were carried out, each consisting on average of 27 papers (range 19 to 49 papers), under conditions of wet bulb depression varying from 2.8 to 7.5°C and at time intervals from $\frac{1}{2}$ hour to 8 hours. In every trial a highly significant correlation was found between wet length and fluid weight in the 5 mm tip (mean correlation coefficient 0.91, range 0.80 to 0.97, $P < 0.001$). The general pattern of results is best illustrated by the findings at a period of 2 hours in the envelopes (Fig. 1). The Schirmer paper wet length is shown plotted against

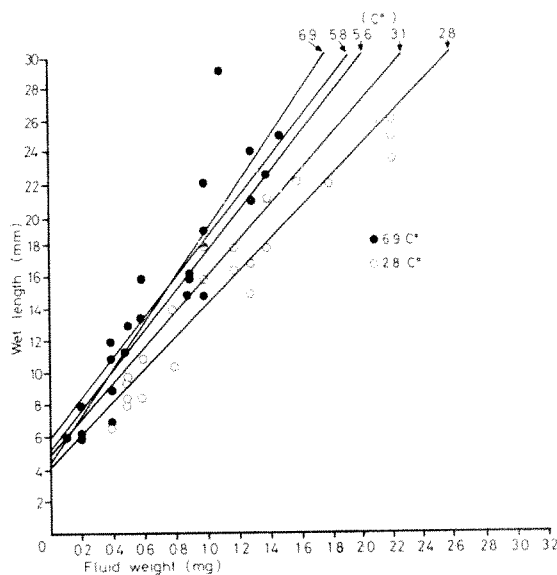


Fig. 1 Two hours. Relationship between wet length and fluid weight in 5 mm tip of Schirmer paper at differing wet bulb depressions (co-ordinates at 3.1, 5.6, and 5.8°C depressions omitted for clarity).

fluid weight in the tip, these 2 hour tests being performed at 5 different wet bulb depressions. It is seen that the moist length is directly proportional to the fluid weight, but that papers moistened at a depression of 6.9°C hold less fluid than those at 2.8°C , this difference increasing with greater wet length. The results at intermediate depressions are seen to lie in order between the highest and lowest depression lines, and it was established that the intervals between these lines related directly to the logarithms of the depressions.

Regression lines were compared statistically by the appropriate F test.⁶ No significant difference was found between the results at $\frac{1}{2}$ hour and 1 hour, but with further lapse of time there was a narrowing of the gap between high and low depression lines. In addition the graph lines were observed to shift to the left, indicating that fluid was slowly being lost from the tip of the paper.

These changes were seen in the 2 hour and 3 hour graphs, and by 4 hours the gaps between the lines at different depressions had closed completely (no significant difference between 4 hour findings at 6.7 , 6.1 , and 3.5°C : the correlation coefficient for total 65 papers was 0.94).

At 5 hours there had been a further shift of the lines to the left, but no subsequent change was found with 6 or 8 hour papers. Thus, while the difference between high and low depression results

had been eliminated at 4 hours, the moisture content did not finally become stable in the paper until 5 hours had elapsed.

During the investigations 17 papers, each moistened to about its full length, were found to hold a disproportionately heavy weight of fluid. These were considered to be 'soaked' papers, the fluid content of which was misleading to the trial, and they were therefore discounted (see Discussion).

Discussion

It has been seen that the rapid drying of Schirmer papers necessitates estimation of fluid content either immediately after the 5 minute moistening period or else after sealing in a container to prevent further evaporation to the atmosphere.

IMMEDIATE WEIGHING

In 3 of the short trials no significant relationship could be demonstrated between wet length of paper and fluid weight in the 5 mm tip, while in the fourth, at 5.3C° depression, a significant relationship was both found and confirmed by extension to a total of 37 papers. Nevertheless, the correlation between the 2 variables was poor, indicating that even in this case it would be unreliable to infer a particular fluid weight from a known moist length. It is possible that more extended trials at other conditions of wet bulb depression would also have produced significant results, but there is no reason to expect the correlation to be any closer.

Bonavida and Sapse³ and Pietch and Pearlman⁴ employed the 5 mm tip of tear-moistened Schirmer strips in lysozyme tests on the assumption that it could be relied upon to hold a constant quantity of fluid. However, in the present work a range of 0.5 to 4.6 mg of fluid has been demonstrated in the limited number of papers tested, and in practice lacrimation producing heavily soaked papers would be likely to give still greater weights. Although the application of unit quantity of fluid to a Schirmer paper may be shown to moisten it to a consistent length,^{3,7,8} it is clear that the converse does not follow and that unit length of paper can hold a wide range of fluid weights.

DELAYED WEIGHING

It was observed that the fluid became stabilised in the paper over a 5-hour period in the envelope. As will be seen later, loss by evaporation within the envelope was slight, and therefore the changes must be accounted for by passage of fluid along the paper. It would seem likely that some form of fluid gradient is present in the Schirmer strip, the moisture lying most thickly at the tip and tapering off to-

wards the dry end, and during the period in the sealed envelope the fluid becomes more evenly spread, although still retaining a gradient when finally stabilised. This could explain both the close relationship between tip weight and moist length and the changes which occur with time. A period within the envelope produces much more consistent results than were found on immediate weighing.

SOAKED PAPERS

It was seen that some papers moistened in the region of their full length at 5 minutes could hold disproportionately high quantities of fluid in the tip. This may be explained on the basis that the paper will accept a large quantity of fluid while being unable to register a wet length greater than 30 mm; also that 5 minutes may occasionally be insufficient for a substantial volume of liquid to reach its expected length of moistening. Hence readings approaching the maximum length must be interpreted with caution. Lysozyme techniques in which soaked Schirmer papers are used⁹ will be subject to particularly uncertain results.

TABLE OF MEAN RESULTS

The findings noted after a period in the sealed envelopes were thought to warrant tabulation of mean results (Table 1). The Table is based on the results at highest and lowest depressions, with logarithmic intervals for intermediate figures. All moist length measurements include the first 5 mm, and any wetting of less than this figure would not be relevant to the present trials.

A previous paper⁵ showed that with filter paper discs moisture could be lost within the container. This factor was therefore examined by serial weighings of 19 envelopes containing moistened Schirmer papers, and the total loss of fluid by evaporation within the envelope and on extraction was found in each case to be 0.2 mg per 5 mm of moist strip. This weight, which in the case of tears would leave lysozyme in the paper, has therefore been added to all results in the formulation of the Table.

In practice, because evaporation from Schirmer papers containing tears will deposit the lysozyme in the strip, some degree of vapour loss from the envelope is unlikely to affect results, provided sufficient moisture remains to permit the changes found in these trials. It is probable, therefore, that glueing of the envelopes is not essential if they have been well sealed with adhesive tape.

It should be noted that all the trials are based on a relationship of low wet bulb depression at a lower temperature, and high depression at a warmer temperature. It is not known whether the findings would hold good under altered circumstances, as,

Table 1 Mean weights of fluid in 5 mm tip after periods in sealed envelope (weights expressed in mg)

Period of time in envelope (hours)	$\frac{1}{2}$ and 1			2			3			4	5 and over
Wet bulb depression (°C)											
Wet length (mm)	3	5	7	3	5	7	3	5	7	3 to 7	3 to 7
6	0.3	0.3	0.3	0.4	0.3	0.3	0.4	0.2	0.1	0.2	0.2
8	0.6	0.5	0.4	0.6	0.5	0.4	0.6	0.4	0.3	0.4	0.4
10	0.9	0.7	0.6	0.8	0.7	0.6	0.8	0.5	0.4	0.6	0.5
12	1.2	0.9	0.7	1.0	0.8	0.7	1.0	0.7	0.5	0.7	0.6
14	1.4	1.1	0.9	1.2	1.0	0.9	1.2	0.9	0.7	0.9	0.8
16	1.7	1.3	1.0	1.4	1.1	1.0	1.4	1.0	0.8	1.1	0.9
18	2.0	1.5	1.2	1.6	1.3	1.1	1.5	1.2	0.9	1.3	1.1
20	2.2	1.7	1.3	1.8	1.5	1.3	1.7	1.3	1.1	1.5	1.2
22	2.5	1.9	1.5	2.0	1.6	1.4	1.9	1.5	1.2	1.7	1.3
24	2.8	2.1	1.6	2.1	1.8	1.6	2.1	1.6	1.3	1.9	1.5
26	3.1	2.3	1.8	2.3	1.9	1.7	2.3	1.8	1.4	2.1	1.6
28	3.3	2.5	1.9	2.5	2.1	1.8	2.5	1.9	1.6	2.3	1.7
30	3.6	2.7	2.1	2.7	2.3	2.0	2.7	2.1	1.7	2.5	1.9

95% Confidence intervals at mean: $\frac{1}{2}$ and 1 hour, 3.6°C–0.88 mm, 6.96°C–0.85 mm; 2 hours, 2.8°C–0.74 mm, 6.9°C–1.13 mm; 3 hours, 2.8°C–0.83 mm, 6.7°C–1.78 mm; 4 hours, 0.62 mm; 5 hours and over, 0.63 mm.

for example, a low wet bulb depression at high temperature.

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Quantitative tear lysozyme assay: a new technique for transporting specimens

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SUMMARY We have developed a method for assaying the concentration of tear lysozyme using eluates of tear fluid collected on filter paper discs. Specimens can be stored and transported to remote laboratories for assay. We have shown that the 'indirect' or eluate method gives statistically comparable results to the 'direct' method using fresh, neat tear fluid.

We have previously described a tear lysozyme assay using tear fluid collected on filter paper discs.¹ Discs must be placed as soon as possible directly on to an agar plate seeded with *Micrococcus luteus* (*lysodeikticus*). The results of the assay have given a reliable guide to lacrimal gland function.² However, the organisation of the test has virtually required that the patient attends the laboratory. This has been inconvenient and has often led to patients travelling long distances.

Hypher³ has criticised the test suggesting that a small amount of the tear fluid collected on to the disc remains in the bottle. He has calculated a correction factor for this.

We have now developed a modified test that allows the collection of tear fluid at a site distant from the laboratory and which minimises any loss of tear fluid from the disc.

Materials and methods

COLLECTION OF TEAR FLUID

Tear fluid was collected on to Whatman No. 1 filter paper discs, 5 mm in diameter, which were placed in the lower conjunctival sac. The volume of tear fluid collected was ascertained by weighing the disc in its bottle before and after collection. For this purpose a portable CAHN* automatic electro-balance was chosen (Fig. 1), as it could be set up

on a desk in an outpatient clinic. It was accurate to ± 0.01 mg equivalent to ± 0.01 μ l tear fluid.

A Hewlett-Packard printing calculator (Model 9751/0) was used, as it was compatible with the output of the balance and could be programmed to calculate and print results of weight readings. Since no bottles were available commercially that were sufficiently small (maximum height 15 mm) or light (maximum weight 1500 mg), our Hospital Physics Department manufactured bottles by injection moulding from polypropylene beads.⁴ A tool-steel mould was made with brass inserts that produced the bottle and lid as a one-piece moulding† (Fig. 2). Each bottle, with lid closed, weighed approximately 300 mg, measured 10 mm high by 11 mm wide and held up to 200 μ l fluid. The bottles were cleaned in an ultrasonic water bath and dried in a hot air oven; a filter paper disc was then placed in each bottle. They were sterilised in batches by 2.5 megarads of irradiation.‡

PREPARATION OF ELUATE

After the bottle containing the tear fluid collected on to the disc had been weighed approximately 100 μ l of phosphate-buffered saline was added from an Oxford pipette with a disposable tip and the lid was fastened. The bottle was reweighed to ascertain the exact volume of buffer added and the result recorded. After collection the bottles were transported at atmospheric temperature and placed overnight in a $+4^{\circ}\text{C}$ refrigerator. Next day they were transferred to a -20°C freezer in the laboratory pending assay.

*Cahn Instruments, Ventron Corporation, 16207 South Carmenita Road, Cerritos, California 90701, USA. Available in UK with Hewlett-Packard printing calculator and R51 balance from Oerling Instruments Ltd, Orpington, Kent.

Correspondence to Dr D. V. Seal, Public Health Laboratory, General Hospital, Southampton SO9 4XY.

†Manumold Mark 2 Injection Moulding Press, Florin Street, 457 Caledonian Road, London N7.

‡Irradiated Products Ltd, Elgin Drive, Swindon, Wilts.

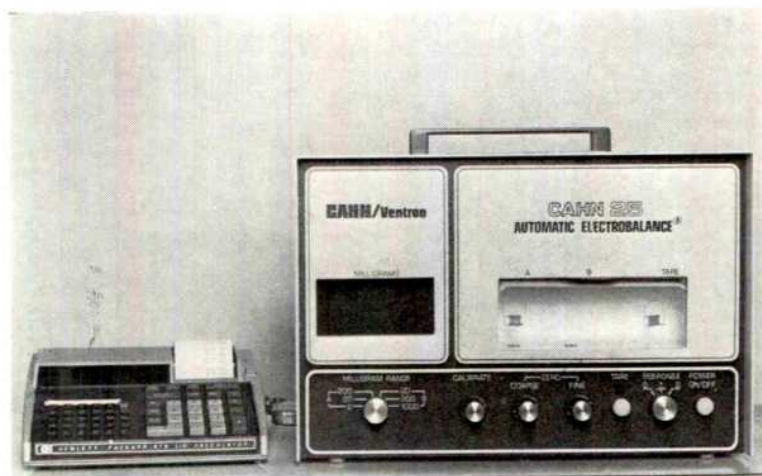


Fig. 1 Portable electrobalance with printing calculator.

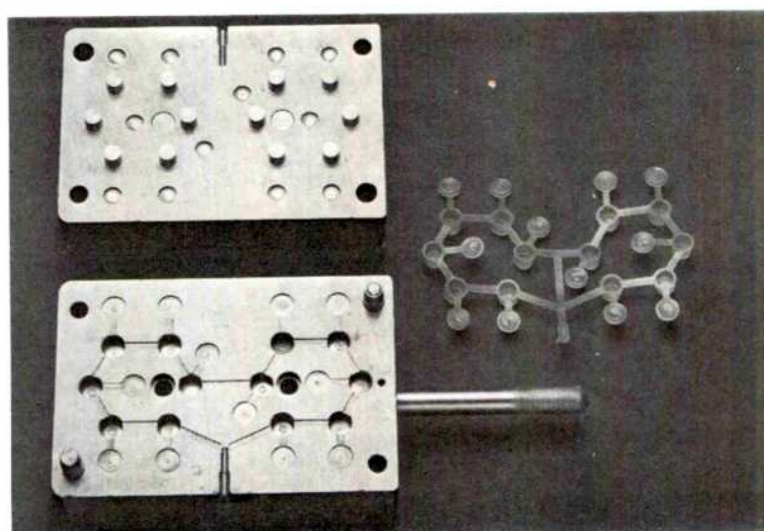


Fig. 2 Injection mould and polypropylene bottles.

PERFORMANCE OF ASSAY

For the assay, similar filter paper discs were prepared in 10×25 mm plastic tubes,* each tube being weighed on an Oertling R51 laboratory balance, accurate to ± 0.01 mg. With the use of forceps 2 discs were dipped separately into the eluate of a tear fluid sample, weighed, and the volume taken up by each disc calculated. Batches of two discs were similarly dipped into 5 standards of hen egg lysozyme† containing 0.05, 0.1, 0.2, 0.3, and 0.4 mg/ml respectively, which were calibrated into units of activity per gram by our original spectrophotometric method.¹ All the discs were placed on

an agar plate, previously flooded with *Micrococcus luteus* (*lysodeikticus*) and incubated at 20°C for 4 days. Zone diameters of bacterial lysis around the discs were measured on an image intensifier and recorded. After assay the eluates were frozen and stored at -20°C .

EVALUATION OF ASSAY

This new 'indirect' method of lysozyme assay was evaluated by sampling tear fluid from the right and left eyes of 42 'normal patients' (that is, patients with glaucoma but with normal lacrimal function clinically) aged from 20 to 79 years, with a mean of 56 years. These results were compared with those obtained by our original 'direct' method from 86 normal volunteers, aged 20 to 85 years, with a

*Metal Box Ltd, 30 Great Guildford Street, London SE1.

†Koch-Light Ltd, Colnbrook, Buckinghamshire.

mean of 50 years. Eight patients with established dry eyes, aged 9 to 70 years, were also tested by the 'indirect' method, and the results were compared with 23 patients with keratoconjunctivitis sicca, aged 42 to 68 years, tested by the 'direct' method.

TEST FOR ANTIBACTERIAL SUBSTANCES

Tear fluid was tested for the presence of antibacterial proteins other than lysozyme, which could theoretically inhibit the growth of *Micrococcus luteus*. Agarose containing antihuman leukaemic lysozyme serum was seeded with the micrococcus. Two discs, each containing neat tear fluid from normal volunteers, were placed on the seeded agarose and incubated at 37°C for 18 hours. Two discs, from the same volunteers, were also placed on seeded agarose which did not contain antilysozyme serum and were similarly incubated.

Results

THE ASSAY

The hen egg lysozyme (HEL) standard had an activity of 24 400 units per gram. This compared with an activity of 30 000 units per gram for our HEL standard acquired in 1975. By expressing all results in units of activity per μl , compensation was made for the 2 standards of different strengths, and results of these methods could be directly compared.

A standard graph was prepared for each plate assay plotting the logarithms of the total quantities (in micrograms) of lysozyme on the discs against the squares of the zone diameters of bacterial lysis (Fig. 3). The concentration of lysozyme in the tear eluate, and hence that in the original tear fluid, was calculated in units of activity per microlitre, and its

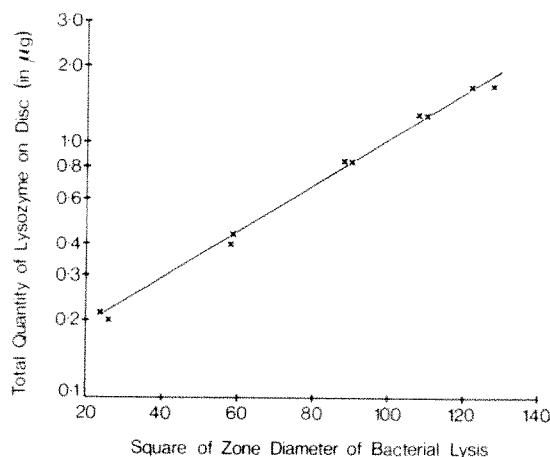


Fig. 3 Calibration graph for plate assay.

relationship to the age of the patient is shown in Fig. 4. The limit of sensitivity for the method was 20 units of activity per μl tear fluid. The mean normal value decreased by 0.5 units of activity per μl tear fluid per year. Values for ± 2 standard deviations (SD) of the means are shown together with the critical lower limit of the 'direct' method of assay which was 1.7 SDs below the mean at any age by this method; values below this limit for any age have only a 5% chance of normality, while values below the 2SD limit have only a 2.5% chance.

In order to make direct comparison between results of patients of different ages, adjustment was made by dividing each result, in units of activity per μl , by the value of the critical lower limit, given

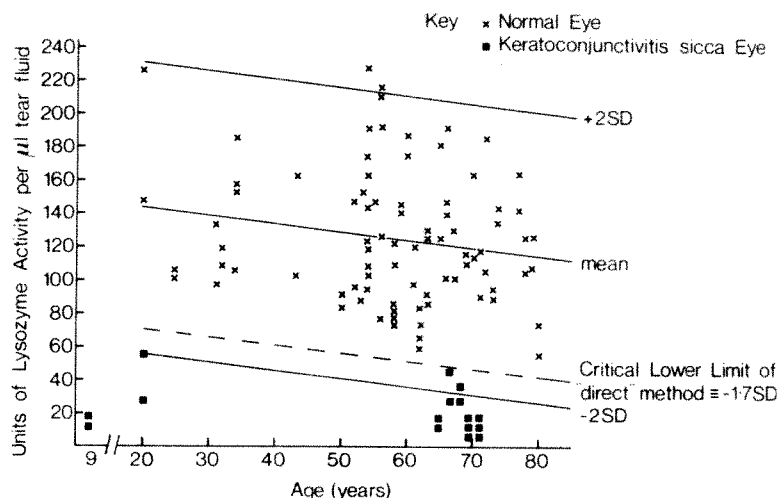


Fig. 4 Lysozyme concentration by age in 42 normal patients and 8 patients with sicca.

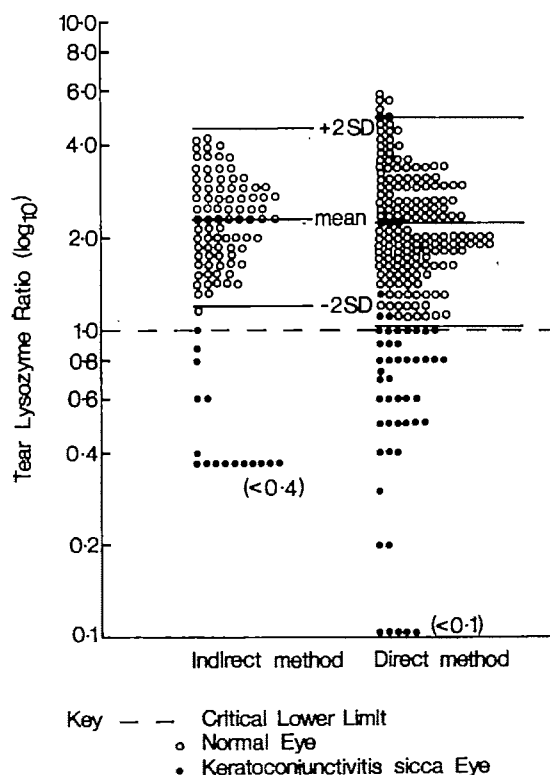


Fig. 5 Distribution of tear lysozyme ratios.

in Fig. 4, for that patient's age (tear lysozyme ratio (TLR)).

EVALUATION OF ASSAY

The distribution of the TLRs for the 'indirect' and 'direct' methods of assay is shown in Fig. 5, where means and SD limits for the normal range are shown, being different to those of Fig. 4 from which they have been derived; the TLRs are expressed on a logarithmic scale. There was no statistical difference between either method for the TLR values obtained from normal patients. At any age the critical lower limit is equivalent to a TLR of 1.0, so that values less than this will have only a 5% chance of normality. The lowest TLR value, and hence tear lysozyme concentration, that can be measured by the 'indirect' method is 0.4, while the lowest value for the 'direct' method is 0.1, because neat tear fluid was placed on to the agar plate resulting in larger zones of bacterial lysis.

For patients with keratoconjunctivitis sicca the TLR results by the 'indirect' method ranged from 1.0 to <0.4 and for the 'direct' method from 1.3 to <0.1. A TLR value of <0.4 is a satisfactory lower

limit for this method, occurring in the patient with clinically established keratoconjunctivitis sicca and indicating that the lysozyme concentration is very low. This has diagnostic and pathological implications.

TEST FOR ANTIBACTERIAL SUBSTANCES

There was no lysis of the micrococcus around the 2 discs on the seeded agarose containing anti-lysozyme antiserum, though immune complex precipitates did occur under the disc, where lysis was also present. There were large zones of bacterial lysis around the 2 discs on the seeded agarose without antiserum. This showed that the tear lysozyme had been prevented from diffusing away from the disc and that there were no proteins present in the neat tear fluid which could inhibit growth of this micrococcus.

Discussion

There are various methods for lysozyme assay. We consider that the 'direct' method we previously described¹ added greatly to the accuracy of the test. Hypher⁶ has shown that the method of Bonavida and Sapse,⁶ whereby a 5 mm piece of a wetted Schirmer strip is cut off and used for the assay, is prone to inaccuracy because of irregular diffusion of tears along the strip. The disadvantage of our 'direct' method is the fact that discs have to be collected in the proximity of the laboratory and processed immediately. Processing can take up to 4 hours and often continues after normal laboratory hours. The 'indirect' method now described permits processing of discs at any time after collection and transportation of specimens to remote laboratories.

It has been pointed out⁷ that there is a diurnal rhythm of tear lysozyme secretion, and we suggest that the discs are collected in the morning or afternoon to achieve maximum values.

The use of live rather than killed *Micrococcus luteus* has the advantage that a nutrient agar plate can be flooded when required and does not need to be prepared in advance. It is a suitable technique for routine use in a hospital laboratory, and sophisticated equipment is not required. The zone sizes obtained are clear to read. We have found no error from other antibacterial proteins known to be present in tear fluid, presumably because their concentration is too low or the *M. luteus* is not sensitive to them.

Lysozyme concentration in transported tear fluid has been studied before, when 1000 Schirmer test strips were posted to a laboratory.⁸ The Schirmer strips had been wrapped in plastic film to preserve their moisture and eluates from them were tested by

filter paper electrophoresis. A study was made of the relative proportions of tear lysozyme, globulin, and albumin with semiquantitation of the tear lysozyme concentrations. However, the paper electrophoresis method is up to 300 times less sensitive than an agarose-micrococcus plate assay, but standard values were not quoted.⁶ Rocket electroimmunoassay is more sensitive than paper electrophoresis but is not recommended for detecting low concentrations of lysozyme.⁹

The normal range of lysozyme concentration by the 'indirect' method has been found statistically similar to that using fresh neat tear fluid (direct method). This indicates that tear lysozyme remains stable when held in solution as an eluate. Abnormally low values have been found in patients with keratoconjunctivitis sicca, similar to those recorded by the 'direct' method, but a lower concentration can be detected by using neat tears. There is no possible loss of tear fluid from the disc as a deposit in the bottle with the 'indirect method' because phosphate-buffered saline is pipetted over the disc in the same bottle to form the eluate. In our earlier studies we found filter paper discs containing neat tear fluid, sealed in bottles, could not be held at +4°C, as they dried out by evaporation within the bottles. The lysozyme molecule is irreversibly damaged at the liquid-air interface when this occurs, and assay values fell considerably.

We envisage the development of enzyme linked immunoassay or radioimmunoassay for measuring the concentration of eluted lysozyme, using specific antiserum. It should be more sensitive, less time

consuming, and would allow the processing of a larger number of specimens.

We thank Merck, Sharpe and Dohme Ltd and the St. George's Hospital Slater Fund for financial assistance with this study. We thank Professor G. R. F. Hilson, Dr D. G. Fleck, and Mr T. Evans for support and for providing us with laboratory facilities. We thank Mr Ray Fautley, Hospital Physics Department, Southampton General Hospital, for manufacturing the mould and polypropylene bottles. We also thank Dr D. R. Gamble for his critical advice and Miss P. J. Stoffell for typing the manuscript.

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Sampling systems for visual field assessment and computerised perimetry

N. DRASDO AND W. C. PEASTON

From the Department of Ophthalmic Optics, University of Aston in Birmingham

SUMMARY Three successive stages in the representations of the visual image are studied by computations from the best available data. The results are embodied in projections, drawn automatically. These projections are related to the assessment of visual disability and the dimensions of lesions in the retina and visual pathway. Fields can be assessed visually with the aid of graticules or directly during computerised perimetry.

The complexity and variability of perimetric data present a serious obstacle to progress in ophthalmology owing to the difficulty in summarising or comparing field changes and assessing visual disability. It has therefore often been proposed that different parts of the visual field should be assigned a specific weighting so that a quantitative score could be obtained by calculation or planimetry.¹⁻⁴

Although some of these methods have won a well deserved popularity, they are based on the clinical judgment of their proposers or on surveys of professional opinion and have the disadvantage that an infinite number of alternative arbitrary proposals can be made. The merits of any one may remain forever a matter of opinion. It seems obvious therefore that there are some virtues attached to methods of quantification which are related to functional properties and dimensions of the visual system and determined by rigorous procedures.

The transformations which the visual image undergoes before it arrives as an encoded pattern of neural events in the cerebral cortex include 3 distinct stages which can be related to perimetric quantification. The image begins in environmental space, when it may be considered to be equally distributed over the solid angle subtended at the pupil by the visual field. It is projected on to the retina already subject to a relative compression of the peripheral regions, and finally in the visual pathways and striate cortex the foveal region has achieved its greatly enhanced representation. Surprisingly, none of these stages is proportionately displayed on the

conventional perimetric chart,⁵⁻⁷ which has retained a dominant role as a result of its use with mechanical self-recording perimeters.

Improved theoretical knowledge and the availability of techniques for more accurate computation and automatic drawing of charts have enabled us to re-examine this subject extensively to embody our findings in speedy and convenient methods of field quantification, and to present some observations on possible applications in computerised perimetry.

Theory and method

THE SOLID ANGLE

The extent of the visual field in terms of its solid angle has specific relevance to visual disability assessment. This may be illustrated by considering the solid angle in cases of contracted visual fields⁸ and is shown by the examples given in Table 1. On entering an unfamiliar room a subject with a contracted field must make a lengthy series of fixations, and orientation, mobility, and the recognition of extended objects or hazards are therefore very dependent on fixation strategy and short-term memory. The solid angle of a visual field is not proportional to its area on the conventional perimetric chart, and a chart which truly represents its size in solid degrees or steradians was described by Doesschatte.⁵ This has been achieved in the chart shown in Fig. 1A by making r , the radius of each circle, satisfy the equation

$$r(\theta) = K \sqrt{1 - \cos\theta},$$

where θ is the angular semidiameter of a polar zone of visual space and K is a constant determining the

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Table 1 *The quantification of various field defects according to the 3 selected criteria produces scores which are essentially independent from each other and from visual acuity*

Scotoma	Percentage loss			
	Solid angle	Retinal area	Channel capacity	Visual acuity
25° Diameter contracted field	96.1	96.4	49	0
10° Diameter central scotoma	0.63	0.58	25	70
Small peripheral detachment	2.3	1.0	0.3	0

size of the chart. The chart was produced on an ICL 1904 digital computer facility by calculating the required radii and then using these values in standard routines for a graph plotter output.

RETINAL IMAGE PROJECTION

The magnification of the image on the retina has long been known to be subject to nonlinearity in the radial direction.⁹ This distortion of the dimensions is greatest in the extreme periphery and may be significant in relation to the observed size of retinal lesions or in the assessment of retinal area for surgical procedures. The nonlinearity was further investigated by Drasdo and Fowler⁷ using a wide-angle schematic eye. The magnification around a circle of constant polar excentricity on the retina was determined. The product of radial and circular magnification was used to estimate the projection of the retinal area related to a solid degree in visual space, and a representative field chart was produced. It subsequently emerged that, owing to an error in formula 4 of Mandell and St Helen,¹⁰ a slight inaccuracy in the ray trace had occurred. This has been corrected, and although the correction has little effect on the retinal area chart it has been revised (Fig. 1B). The new equation for the corneal surface was $y^2 = 15.6x - 0.75x^2$, and the reciprocal of the derivative of this equation provided the tangent of the angle for the ray trace in the manner originally described. The modified chart permits an accurate estimate to be made of the size of a retinal area and may be useful for correlation with other data in surgical or electroretinographic studies.

NEURAL REPRESENTATION AND INFORMATION CHANNEL CAPACITY

The neural representation of the visual field at the level of the retinal ganglion cell layer, in the visual pathways, and striate cortex can be described by equations.¹¹ Quantification of the field in such terms is clearly valuable since it relates to the amount of

neural damage at a specified point in the visual pathways. The total information intake, or channel capacity, of an eye¹² can be estimated by using the same equations¹¹ to determine the number of bits per solid degree at any point in the visual field and integrating these values. The equations therefore provide a system of quantification which is of particular relevance to neuro-ophthalmological studies and perhaps the most generally valuable criterion of visual capability. This possibility was to some extent anticipated by Doeschate⁵ in his somewhat tentative proposal of a chart based on integrated visual acuity, and by Crick,⁶ who commented on the ideal of a projection based on cortical area. For the purposes of the present study the calculation was based on information channel capacity but the quantification is in percentage terms which may be equally applied to neural representation.

The maximal potential information density $D(\theta)$ in bits per solid degree at any excentricity θ on a principal meridian of the visual field can be estimated from the following expression based on a more general equation.¹¹

$$D(\theta) = 3600 (0.6 [1 + s\theta \{1 + 3\theta^2 \times 10^{-5} + 8(s\theta)^{5.5} \times 10^{-10}\}]^{-2}) \dots \dots \dots (1)$$

where s is (0.46–0.000430), (0.50+0.00190), 0.62+0.00330) or (0.66–0.00060) for the temporal nasal superior and inferior portions of the principal meridians.

The solid angle $\Omega(\theta)$ subtended by any narrow concentric annular zone of visual space, which has a mean excentricity of θ , and inner and outer limits separated by $\Delta\theta$ is given by

$$\Omega(\theta) = \frac{360^2}{2\pi} \left[\cos\left(\frac{\theta-\Delta\theta}{2}\right) - \cos\left(\frac{\theta+\Delta\theta}{2}\right) \right] \text{solid degrees} \dots \dots (2)$$

The maximum information content $i(\theta)$ in any such annular zone is therefore $\Omega(\theta) \cdot D(\theta)$, the product of the values obtained from equations (1) and (2).

The cumulated maximal information content $I(\theta)$, for a visual field enclosed by an outer angular radius of θ is thus given by

$$I(\theta) = \sum_{n=1}^K \Omega(n \cdot \Delta\theta) D(n \cdot \Delta\theta) \dots \dots \dots (3)$$

where $K = \theta/\Delta\theta$.

During the process of numerical integration of $I(\theta)$ for the total field the program was arranged so that, whenever $I(\theta)$ reached certain predetermined amounts, the value of I and θ were stored and a quantity proportional to $\sqrt{I(\theta)}$ for these values

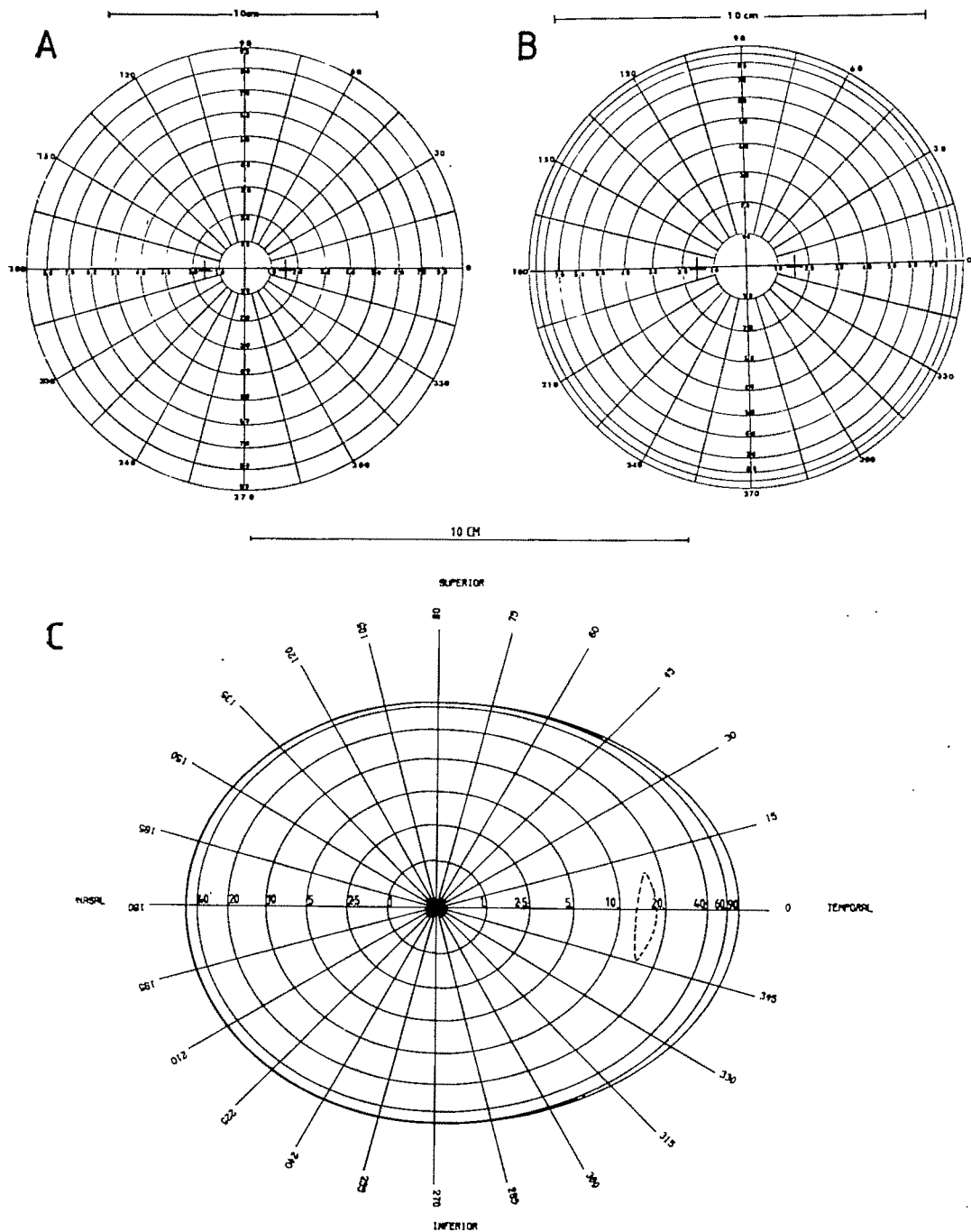


Fig. 1 Perimetric projections in which the visual field is proportionately represented according to 3 selected criteria: (A) the solid angle; (B) the retinal area; (C) information channel capacity and neural representation (right eye chart). Planimetry of plotted fields provides a percentage score ($1\% = 1 \text{ cm}^2$).

was used as the radial distance for lines on a perimeter chart. Since, however, equation (1) gives different values for each meridian of the visual field, the series of radii for each quadrant were used as the semiaxis dimensions in standard ellipse plotting routines of the computer. Each enclosed area on the chart produced by this program was proportional to its maximal information intake and the neural representation of the corresponding part of the visual field (Fig. 1C).

The nonlinear field charts (Figs. 1A, B, and C) can be used to assess visual fields quantitatively by planimetry of affected or surviving areas. But for speedy assessment of visual fields for clinical or research purposes a different approach is required. Esterman² provided a rapid method of quantification in the form of grids which could be applied to conventional perimetric charts.

To produce grids based on the 3 selected criteria, the computer was programmed to divide the visual field into cells of differing area, but equal weighting, according to each criterion, and to draw these superimposed on a conventional perimetric projection. This was achieved by similar numerical integration methods to those used to generate Figs. 1A, B, and C. But in the case of Fig. 1C, which was concerned with the highly asymmetric distribution of information channel capacity, or neural representation, the calculation from equation 1 was performed along oblique meridians as well as along the major ones, the values of s being found by interpolation from the parameters of the two adjacent 90° meridians and processed appropriately in a specially contrived program which culminated in the automatic drawing as previously described.

The cells in the grids were found to be a perceptual distraction when placed on top of the standard charts and were therefore removed, only a central dot being left to represent each 1% unit. These 1% cells were, however, initially constructed by the computer in smaller units, so that some freedom of choice was allowed to ensure that the composite 1% cell could be selected with the central dot in alternative positions. This limited degree of freedom in choice of the position of the dots, without varying their quantitative significance, permitted us to take account of anatomical and diagnostic factors such as the most probable discontinuities in retinal conditions or lesions of the visual pathway. The dot patterns which resulted are displayed in Figs. 3A, B, and C.

It was considered that Figs. 2 and 3 were worthy of separate reproduction in the form of transparent graticules, since the cell charts permitted a fairly precise assessment of small isolated areas, whereas

the dot charts provided a very quick method of assessing widespread field defects.

Discussion

The 3 criteria, based on projections of the visual image, are considered useful because of their independence and apparent validity. They are independent because the score on one criterion can never be predicted from another unless the actual field data are known. Their validity is considered to be axiomatic. If one is concerned with the assessment of visual disability resulting from the amount of field loss, the solid angle criterion is clearly valid. Since most vision during mobility is concerned with grossly super-threshold objects, it is primarily the actual size of the field that is involved. On the other hand, if one is concerned with the amount of visual information, the independent criterion of channel capacity commends itself. Neither of these displaces the importance of visual acuity, and the behavioural correlation of all are worthy of further examination in epidemiological studies on impaired vision.

When considering the assessment of retinal lesions, or of the percentage of retina involved for example in photocoagulation therapy,¹³ it is difficult to dismiss the validity of the retinal projection. The particular value of the neural representation criterion is evident when considering any lesion in the ganglion cell layer, visual pathways, or striate cortex. This might be used in conjunction with the neuroanatomical schemes¹⁴ showing the approximate projection along the optic nerve and radiations to assess the location and extent of a lesion more accurately at any specified point. It has also been appropriately applied to field studies of hereditary optic atrophy.¹⁵ If the independence and validity of the criteria are accepted, it might still be argued that they are not sufficiently different from existing methods to justify their use. This suggestion does not bear close examination, however, and even where the differences are small it would appear advantageous to use these appropriate criteria in order to gain the highest possible correlations in statistical terms where a particular hypothesis is being pursued.

The relationship of the criteria described to many existing methods of quantification is shown in Table 2. This emphasises previous views^{5,6} that the conventional chart does not represent any important criterion of the visual field appropriately. It can be seen that every criterion displayed shows a greater representation of the central area than the conventional perimetric chart. This must lead to the suggestion that the designers of computerised perimeters should display the data appropriately. The central

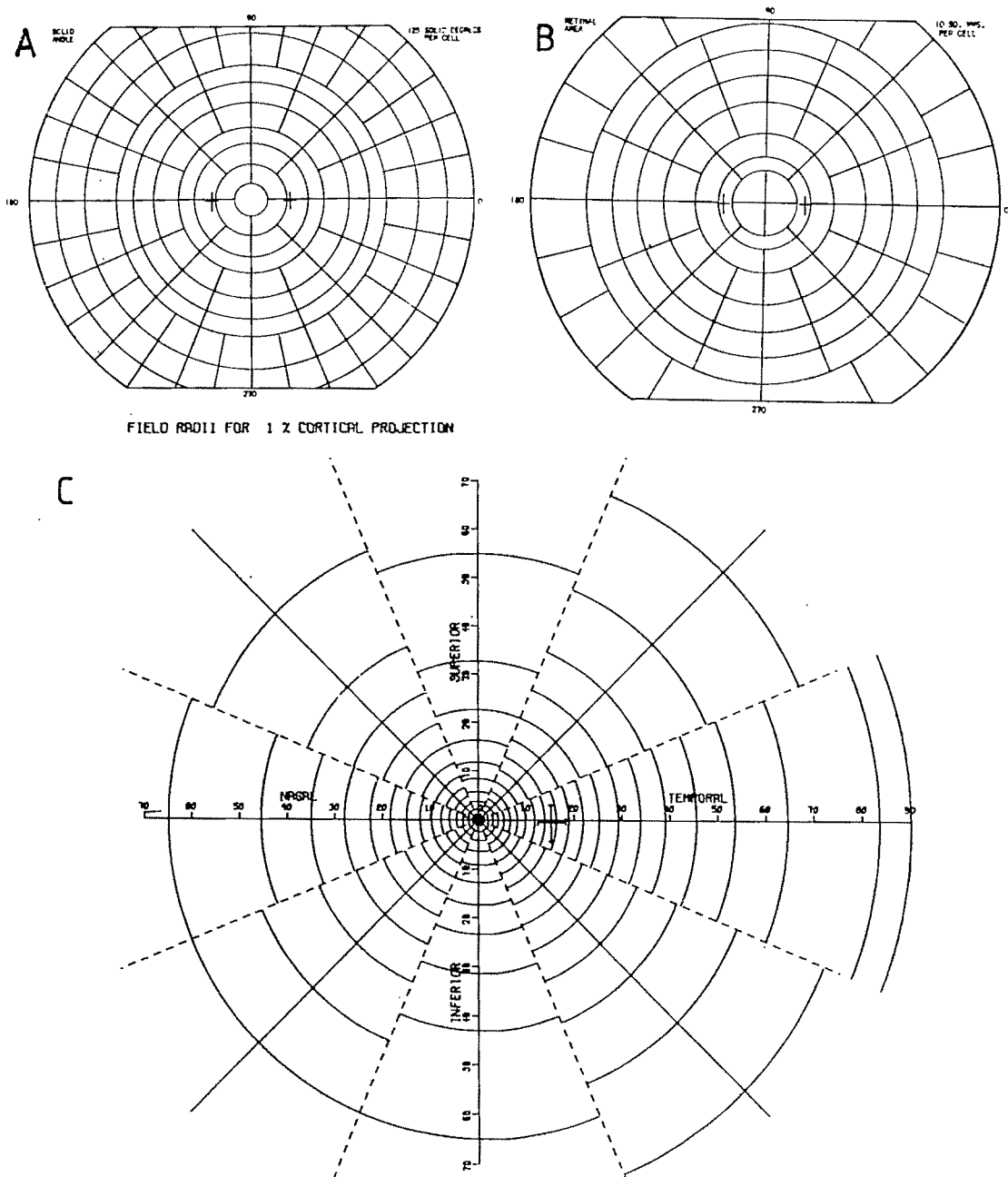


Fig. 2 Graticules for the assessment of fields plotted on conventional charts. (A) Each cell corresponds to 1% of the total solid angle. (B) The cells correspond to percentage units of functional retina, of which some 25% may be obscured by facial contours. (C) Channel capacity or neural representation. The computer, programmed to divide each octant into 1% annular sectors, created $\frac{1}{4}$ % cells around a central 4% circle and added the limits of the visual field.

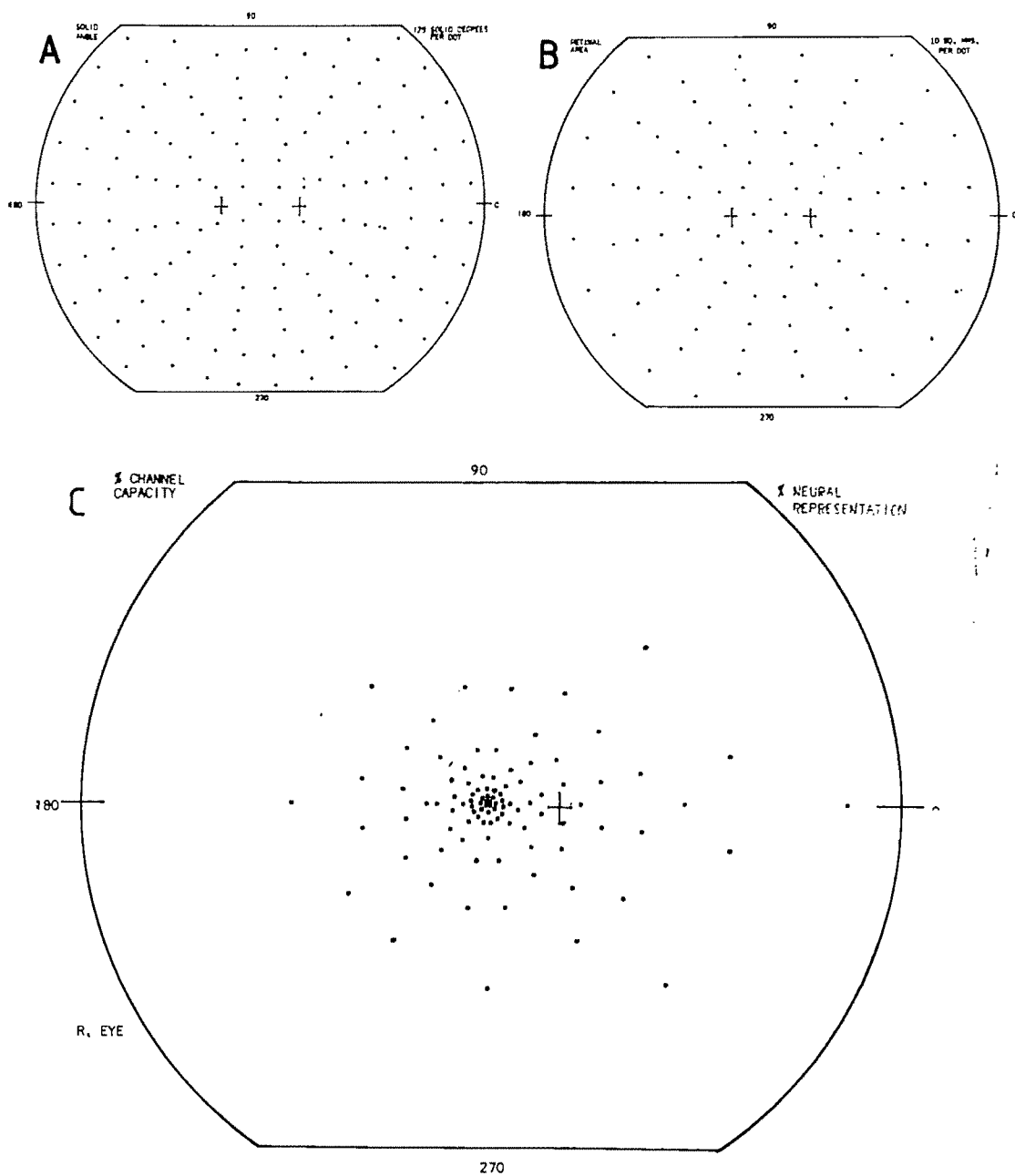


Fig. 3 Dot graticules for speedy assessment of conventional field plots. Each dot scores as 1%.

Table 2 The percentage weighting falling within a given peripheral angle according to various field charts and assessment schemes. Note that every system of quantification gives a greater representation to the central fields than does the conventional field chart.

Weighting criterion	Radial peripheral angle			
	10°	20°	40°	70°
Conventional chart (area)	2.12	8.47	33.86	79.26
Solid angle	2.53	10.06	39.03	85.78
Retinal area	3.33	12.90	47.29	90.96
Walker (non-lin.)	3.69	12.30	43.67	86.85
Esterman grid	6.00	27.00	62.00	92.00
Crick (parabolic)	10.86	31.58	67.38	94.08
Spaeth <i>et al.</i>	15.39	30.77	61.54	94.23
Collenbrander	16.00	32.00	64.00	94.00
Channel capacity	45.16	67.37	90.23	99.65

portions of the field can be represented on a large scale when no mechanical linkage is necessary. The parabolic projection of Crick⁶ may well approximate towards a useful distribution of the displayed data, but the information in Fig. 2 provides a basis for suitable designs. Both central and peripheral fields can be adequately portrayed on such nonlinear charts without any increase in the total size of the record and with the minimal morphological distortion to which clinicians can easily adapt. In any event the emergence of more sophisticated computerised perimeters will permit the provision of several options in chart display.

Such systems could easily be programmed to utilise the sampling points shown on the graticules of Fig. 3 and to assess the criterion scores directly. This, however, might constitute an excessive extension of clinical procedures, so that the more appropriate strategy may be to organise the program to estimate each criterion as nearly as possible when any particular array of diagnostic sampling points is used. Estimates for the 3 criteria could then be printed out automatically on every perimetric record produced by a computerised system, independent of the particular diagnostic series used in the examination. The problems of visual estimation would thereby be effectively simplified and the data would be readily available on all records for statistical correlations. The data presented in Fig. 2 may thus assist instrument designers in incorporating advantageous features in computerised perimetry systems.

The present proposals relate to the distribution of weighting in the visual field but stop short of a complete system of quantification for disability assessment. They are clearly applicable to absolute scotomas, but the long-standing problems of

quantification of relative scotomas and binocular fields still require a solution, which is in the present state of knowledge essentially arbitrary. In accordance with conventional practice, however, a 3/330 target seems appropriate for solid angle assessment, and this could be applied binocularly. Similarly it appears that, if a relative scotoma is regarded as absolute when the target diameter is more than 3 times the normal value, the error in channel capacity assessments will probably be negligible.

Conclusions

Computer programs have been used to carry out calculations on visual fields and draw projections automatically. Three projections were selected for their functional significance and potential clinical value. These were based on (a) the solid angle of the visual field; (b) the projection of the field on the retina; (c) the information content of the visual field and its neural representation. Planimetry of the chart area permitted quantitative assessment on the basis of these criteria.

To avoid the tedious process of quantification the computer was used to prepare alternative projections in the form of graticules for speedy assessment of conventional field charts.

For disability assessment it was considered that projections (a) and (c) were most likely to be useful and less arbitrary than many established criteria. Criterion (a) was considered to relate to mobility where vision is mostly at grossly suprathreshold levels. Criterion (b) seemed the obvious criterion of overall visual capability (relating to tasks involving a large proportion of the channel capacity in normal vision, such as the location of objects). It was considered to be independent of visual acuity (which related to the observations of small isolated objects already located). For diagnostic and research purposes criteria (b) and (c) were considered most useful owing to their unprecedented facility for revealing the extent of lesions in the retina, visual pathways, and striate cortex.

It was concluded that it would be advantageous to incorporate an estimate of the scores for the 3 criteria in the printout of computerised perimetry systems. It also appeared appropriate that such field plots should be displayed on nonlinear charts.

Our thanks are due to Professors G. F. A. Harding and S. J. Crews for encouragement to bring this report to publication, and to the West Midland Regional Health Authority for support for W.C.P.

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Static perimetry in the study of amblyopic scotomata

D. P. AGGARWAL AND GOPAL VERMA

*From the Department of Ophthalmology, University College of Medical Sciences,
and Safdarjang Hospital, New Delhi, India*

SUMMARY A visual field study of 50 cases of unilateral functional amblyopia revealed a relative central scotoma of 2-10° width and 0.1 to 0.8 LU (log units of neutral density filters) depth in 29 out of 50 cases by static perimetry, while kinetic perimetry revealed a central scotoma in only 3 cases of paramacular fixation. In the majority of cases the eccentric area of fixation lay on the edge of the amblyopic scotoma, and it was identical to the point of peak retinal sensitivity.

The consensus of opinion is that reduction of foveal function by a suppression scotoma influences the development of fixation anomalies in amblyopic eyes. Amblyopic scotomata have been studied by several workers using different perimetric techniques, but the results are not in agreement, and the development of central inhibitory scotomata is also disputed. Thus Cuppers¹ considers the development of amblyopic scotomata to be a pathological exaggeration of local adaptation (Troxler's phenomenon) based on field charting studies of amblyopic patients by static perimetry, and he found that the sensitivities obtained by static perimetry were inferior to those obtained by kinetic perimetry. Cuppers's view was supported also by Francois *et al.*² On the other hand Mackensen,³ using the static perimetry technique, proved that in eccentrically fixing eyes the scotoma is deepest at the level of the abnormal fixating point, where sensitivity is inferior to that of fovea fixation point. He found static perimetry to be superior to other methods of visual field charting in amblyopic patients.

The present study was undertaken to compare the results of static and kinetic field charting in amblyopic patients and also to compare the retinal light threshold values in the area of eccentric fixation and in the region of foveal fixation of the same eye by means of static perimetry.

Material and methods

Fifty patients with unilateral functional amblyopic and visual loss of more than 2 lines as compared with the fellow eye (i.e., 6/12 or below with full refractive correction and no detectable fundus

pathology) were selected from the Amblyopia and Squint Clinic of the Ophthalmic Department, Irwin Hospital, New Delhi.

The age of the patients ranged from 7 to 35 years. In all cases selected for study a detailed history regarding age of onset of amblyopia or squint, nature of deviation, and any previous treatment in the form of glasses, orthoptics, pleoptics, or surgery was recorded. In all cases after retinoscopy and fundus examination under appropriate cycloplegia glasses were prescribed and visual acuity determined by Snellen's optotypes. The type of fixation pattern and degree of eccentricity were determined in all cases by the graticule incorporated in Heine's ophthalmoscope. Only cases of central fixation and cases with steady eccentric fixation were selected for field charting. Field examination was done with a white target size II (1 mm²), luminosity 4, on Goldmann's perimeter. Static perimetry technique was employed for the amblyopic as well as for the normal eye on Goldmann's perimeter with a static attachment using target size II and a background illumination 31.5 apostilb.

The target was presented thrice for 1 second at intervals of 3 seconds in order to avoid local adaptation (Troxler's phenomenon). The meridian which we had examined by static perimetry technique passed through the foveal fixation point of the amblyopic eye and the eccentric area of fixation in cases of eccentric fixation, whereas in cases of central fixation the meridian passed through the foveal point on the 0-180° axis. The target luminosity was recorded on the 0° meridian, and this luminosity was the light threshold of the foveal fixation point or the eccentric area of fixation, depending on whether the patient had foveal or eccentric fixation. The differential light threshold for a white target

size II was thus recorded for the following points 0, 1, 2, 3, 5, 10, 15, 20, 25, 30, 40, 50°. The borders of the blind spot and the scotomata were examined degree by degree. The width of the scotomata was measured in degrees from one edge of the crater to the other on the horizontal diameter. The depth of the scotoma was measured in terms of log units of neutral density filters (LU).

Results

AMBLYOPIA WITH FOVEAL FIXATION

In all 25 cases of central fixation a routine monocular kinetic central field charting failed to reveal any defect.

The static perimetry technique revealed a definite lowering of the light threshold curve in the amblyopic eye as compared to normal eye, with marked depression of retinal sensitivity at the fovea of the amblyopic eye in all cases. The depression of retinal sensitivity was directly proportional to depth of the amblyopia (Fig. 1).

A central relative scotoma of 2–8° was detected in 11 out of 25 cases (44%).

The depth of the scotoma varied from 0.1 to 0.8 LU. The central relative scotoma was deepest at the position of foveal fixation in the majority of cases (Fig. 2).

AMBLYOPIA WITH ECCENTRIC FIXATION

A routine kinetic central field charting revealed a relative scotoma of 3–4° within an area of 5° around the foveal fixation point in only 3 of 25 cases (12%).

Static perimetry technique showed scotoma of 2–10° in 18 out of 25 cases (72%) inclusive of 3 cases detected by kinetic perimetry (Fig. 3).

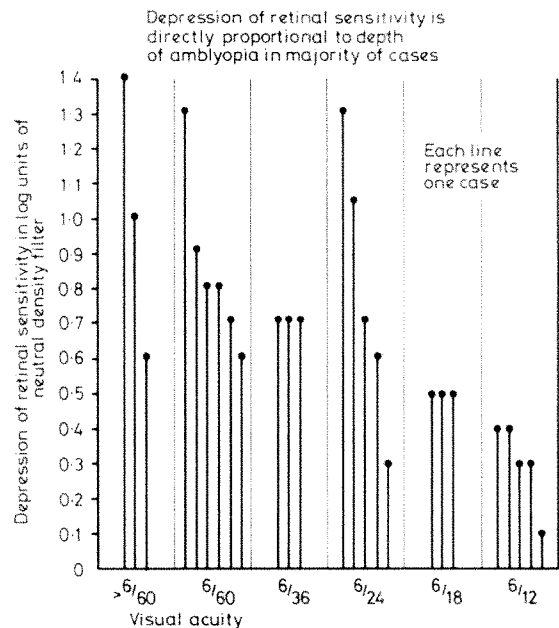
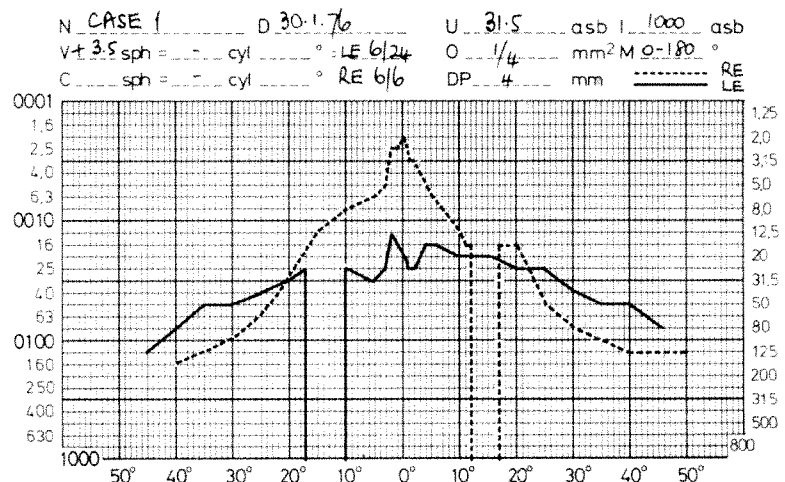


Fig. 1 Relation between depth of amblyopia and depression of retinal sensitivity in static perimetry.

In 13 out of 18 cases (72.2%) which showed scotomata the point of eccentric fixation was lying on the edge of the scotoma. In 16 out of 25 cases (64%) the sensitivity of eccentric point chosen for fixation by the amblyopic eye was higher than that of the foveal fixation point of the same eye. In 7 cases (28%) the fovea of the amblyopic eye was more sensitive than the eccentric area of fixation and had predominance over all other retinal points. Only in 2 cases (8%) was the peak of retinal sensi-

Fig. 2 Static perimetry chart of an amblyopic patient (fixation-foveal) showing depth of scotoma 0.2 LU and width of scotoma 4° (LU=long units of neutral density filter).



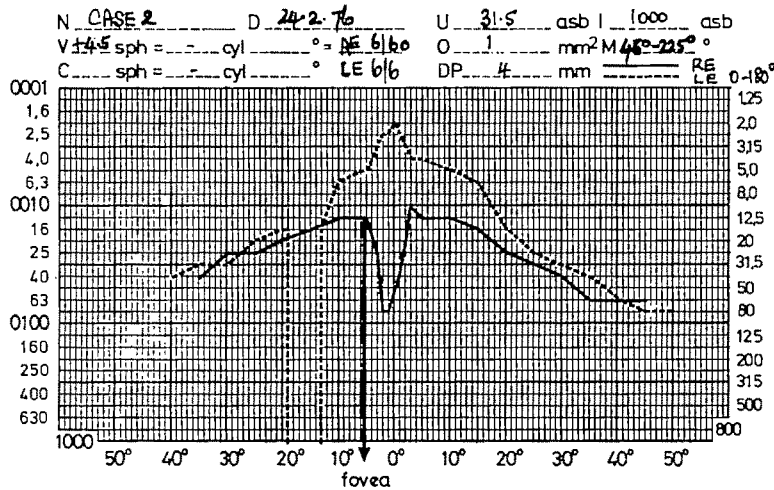


Fig. 3 Static perimetry chart of an amblyopic patient having paramacular fixation. Depth of scotoma 0.8 LU and width of scotoma 8°.

tivity of the eccentric point of fixation equal to the foveal point of fixation of the amblyopic eye (Fig. 4).

Discussion

The pattern of central visual loss in amblyopia ex-anopsia has been studied by Mackensen.³ He has shown a very slight central relative scotoma of only 2-4° in diameter under monocular testing with normal sensitivity levels elsewhere. The area of eccentric fixation could not be identical with the

area of highest light sensitivity, that is, the peak of retinal sensitivity did not coincide with the point of eccentric fixation.

A similar study was done by Blatt and Regenbogen.⁴ These authors found a complete scotoma to white and to colours corresponding to the macula in all cases of eccentric fixation using monocular scotometry. Other authors, such as Pasino and Mariani,⁵ claim that a central scotoma is present in only a few cases and then almost uniquely in marked strabismic amblyopia with eccentric fixation

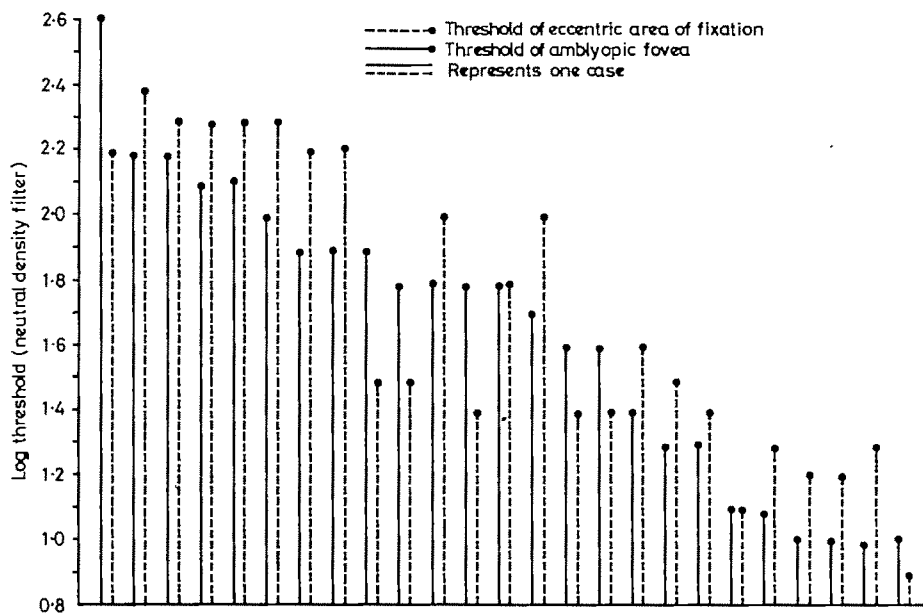


Fig. 4 Relation between sensitivity of eccentric area of fixation and fovea of amblyopia eye.

under monocular testing. An increase of differential light threshold in all the retinal points tested at 25° from the centre was also reported by these authors.

In the present study a relative scotoma of 3–4° could be detected in only 3 out of 25 cases of amblyopia with paramacular fixation by means of monocular kinetic perimetry, while no scotoma was found by kinetic perimetry in 25 cases of amblyopia with foveal fixation.

The following conclusions are drawn from our study: (1) Routine kinetic perimetry has no role in field charting of amblyopic patients in cases of central fixation. (2) Static perimetry is a better technique for field charting in amblyopic patients. (3) The observation that the eccentric point of fixation lay on the edge of the scotoma, and the sensitivity of eccentric area chosen for fixation by the amblyopic eye was superior to the point of foveal fixation in the same eye, provides a better understanding of the role of suppression scotomata in

the aetiology of eccentric fixation as proposed by von Noorden.⁶

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Iridocycloretraction in closed-angle glaucoma

P. D. BLACK

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SUMMARY A small series of patients who underwent iridocycloretraction between 1969 and 1976 is analysed. All patients had previously undergone peripheral iridectomy for primary angle-closure glaucoma, and all had 360° of peripheral anterior synechiae, as seen with the gonioscope. It was found that iridocycloretraction was successful in an unacceptably low percentage of cases, and its success was related to whether subconjunctival drainage was established. There was no clinical evidence to support the theory that its main mode of action was to permit access of aqueous to the trabecular meshwork. Therefore it has no practical advantages over other procedures which establish subconjunctival filtration.

In 1969 Krasnov¹ described the technique of iridocycloretraction and defined the prime indication for its use as cases of organic closed-angle glaucoma, that is, those cases in which the angle is closed with peripheral anterior synechiae. Subsequent reports of its use are sporadic and concerned mainly with aphakic glaucoma, as an adjunct to cyclodialysis^{2,3} and in secondary closed-angle glaucoma.^{4,5} There is one large series reporting the results of iridocycloretraction in closed-angle glaucoma, that of Krasnov himself.⁶ In this series he described a success rate of 80% at first operation, rising to 90% after a second procedure. Moreover he postulated that it acted by allowing access of aqueous to the trabecular meshwork by opening the angle between the scleral pillars that were inserted into the anterior chamber. Although he considered the possibility of conventional drainage, he thought that this was not the case in the majority of his successful patients.

A small number of patients who underwent iridocycloretraction for closed-angle glaucoma, without pupil block, in Addenbrooke's Hospital have been assessed.

Materials and methods

Control of glaucoma is defined as maintenance of the central visual field of the patient as measured with the 2 mm and 5 mm white targets on the Bjerrum screen at 2 metres, and no increase in optic disc cupping. While the intraocular pressure is used as an indicator of control, it is not relied on to

Table 1 *Complications of iridocycloretraction (12 cases)*

Hyphaema	6
Uveitis	2
Malignant glaucoma	1

indicate lack of control except when it remains at an unacceptably high level.

Twelve eyes underwent iridocycloretraction in 11 patients. All were Caucasians, aged between 42 and 72 years, with an average age of 62 years. The patients had presented with either acute closed-angle glaucoma (4 cases), intermittent closed-angle glaucoma (2 cases), or chronic closed-angle glaucoma (6 cases), and all had peripheral iridectomy as their primary procedure. All patients underwent iridocycloretraction as described by Krasnov⁶ with the insertion of 2 scleral pillars, except for 1 patient who had 3 scleral pillars inserted. During 1979 the patients were reassessed, and, as well as routine follow-up of central visual fields, intraocular pressure, and optic disc cupping, the following pertinent observations were made: (a) complications of the procedure, early and late; (b) control of the glaucoma; (c) postoperative gonioscopic appearance; (d) presence or absence of a drainage bleb. The duration of follow-up was between 9 years and 3 years, with an average of 3 years 11 months.

The complications of iridocycloretraction are set out in Table 1. It is not surprising that hyphaema occurred in 50% of cases. It is a well-recognised complication of cyclodialysis, which forms part of the procedure, and its occurrence has been commented on before.⁴ In none of these cases was the

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hyphaema of sufficient severity to cause alarm, and it resolved spontaneously in all cases. Uveitis occurred in 2 cases and was severe enough to warrant subconjunctival steroids in 1 case. An exudative reaction around the scleral pillars as described by Aviner² was not seen. Malignant glaucoma occurred in 1 patient and developed within a few days of the procedure. This patient also had a drainage bleb in this eye following iridocyclorotation. He had, interestingly, developed malignant glaucoma in the fellow eye after a peripheral iridectomy, prior to his iridocyclorotation and had required a lens extraction in that eye to control the malignant glaucoma. To control his glaucoma he requires continuous cycloplegia in the eye that has undergone iridocyclorotation.

Iridocyclorotation was not particularly successful in the control of the glaucoma, as Table 2 shows.

Only 33% were controlled without any further medication. A further 33% required the addition of eye drops (one of whom requires continuous cycloplegics), and a further 33% required another surgical procedure within 12 months of the iridocyclorotation. Of these last 4 patients 2 have had trabeculectomies and 1 a cyclodialysis, with success, and 1 has declined further surgery. It is of interest to try to establish why those patients who required no further treatment had successful operations. In this respect the gonioscopic appearance (Table 3) and the presence or absence of a drainage bleb (Table 4) are important.

As can be seen from Table 3, in only 2 cases was the angle maintained open between the pillars, and in 1 of these cases the operation was considered to have failed. This is in marked contrast to the results of Krasnov,⁶ who opened the angle, between scleral pillars, in 128 out of 141 cases. Small clefts were seen around the scleral pedicles in 3 out of the 4 successful cases and in 1 of the failures. The angle

Table 2 *Control of glaucoma after iridocyclorotation*

Completely controlled	4
Required further medications	4
Required further surgery	4
Total	12

Table 3 *Gonioscopic appearance after iridocyclorotation (12 cases)*

	Successful	Requiring drops	Failures
Angle open between pillars	1		1
Clefts around pillars	3	2	
Angle closed		2	3

Table 4 *Presence of a drainage bleb after iridocyclorotation (12 cases)*

	Successful	Requiring drops	Failures
Bleb present	4	1	
Bleb absent		3	4

was closed between the pillars in 3 out of the 4 cases that failed. As can be seen from Table 4, the presence of a drainage bleb was clearly related to the success of the operation. The 1 patient who developed a bleb and then required further medication was the patient with malignant glaucoma, who has now been maintained on cycloplegic drugs for over 4 years.

Discussion

The management of patients with closed-angle glaucoma often presents difficult clinical problems. Peripheral iridectomy has been widely regarded as the treatment of choice, at least initially, but in a significant number it fails to control the glaucoma,⁷ and they require a further surgical procedure. There has been a reluctance to embark on conventional drainage surgery in these patients because of the fear of malignant glaucoma and the subsequent problems in management. Trabeculectomy, though regarded as a very controlled procedure so far as permitting fall of intraocular pressure is concerned, is nevertheless now regarded as a conventional drainage operation, and malignant glaucoma has been known to follow trabeculectomy (Cairns, personal communication).

In his description of iridocyclorotation Krasnov⁶ maintained that it worked by opening the angle between the pillars and permitted a more physiological egress of aqueous. In support of this theory he quoted experimental work on rabbits by Lakomkin⁸ and a report on 1 eye obtained post mortem 3 months after the performance of an iridocyclorotation.⁹ He considered that, while alternative routes of aqueous egress may be formed, either into the suprachoroidal space or into the subconjunctival space, in the majority of his cases normal rates of aqueous flow would be restored, that is, via the trabecular meshwork. If this were the case it would have an obvious attraction in cases of closed-angle glaucoma, in that the iris-lens diaphragm would be less likely to move forward and the risk of malignant glaucoma would be minimised.

A small number of patients have been examined who have undergone iridocyclorotation for chronic closed-angle glaucoma, without pupil block. Whatever the theoretical attractions of iridocyclo-

retraction, the operation in our hands works by establishing subconjunctival drainage, and the success of an operation requires the formation of a filtering bleb. There is no clinical evidence in our series that iridocycloretraction restores normal pathways of aqueous flow from the eye. In our view iridocycloretraction has no advantages over trabeculectomy, which has a considerably higher rate of success.

I am grateful to Mr J. E. Cairns and Mr P. G. Watson for permission to examine their patients and for advice and criticism.

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Trabeculectomy combined with cataract extraction: a follow-up study

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SUMMARY Fifty-nine eyes undergoing combined cataract extraction and trabeculectomy were studied. The follow-up period ranged from 6 months to 2 years. The visual outcome and post-operative control of intraocular pressure have been compared in chronic open-angle, chronic closed-angle, and secondary glaucoma. Good results were obtained in both primary open- and closed-angle glaucoma, but not in secondary glaucoma.

The aim of this retrospective study was to assess the outcome of combined cataract extraction and trabeculectomy, and to determine whether it is a safe, effective procedure for patients in whom cataract and glaucoma coexist.

Trabeculectomy has been shown to be a safe, effective operation in both open- and closed-angle glaucoma^{1,2} and to a lesser extent in secondary glaucoma.³ A small study by Thyer and Wilson⁴ reported encouraging results when trabeculectomy was combined with cataract extraction for glaucoma patients with lens opacities. Further follow-up studies^{5,6} confirmed the efficacy of this procedure, but numbers were small in the first study, and the period of follow-up was only 3 months in the second.

Material and methods

This paper reports the operative and follow-up findings in 47 patients (59 eyes) operated on between April 1974 and June 1978 at the Birmingham and Midland Eye Hospital by consultant staff and junior staff in training. The 59 eyes have been followed up for a minimum of 6 months; of these, 51 have been followed up for 12 months and 28 for 2 years. Most of the patients were over the age of 60 years (age range 23-87 years; mean age 69 years).

Three types of glaucoma were studied; primary open-angle glaucoma, chronic closed-angle glaucoma, and secondary glaucoma (Table 1). Pre-operative assessments of glaucoma control (Table 2) and visual function were compared with those obtained postoperatively.

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Table 1 Breakdown of preoperative diagnosis

Diagnostic category	No. of eyes
Primary open-angle glaucoma	29
Chronic closed-angle glaucoma	19*
Secondary glaucoma	11†
Total	59

*Peripheral iridectomy previously performed in 7; angle closure from a congenital angle anomaly in 2. †Nine eyes with uveitis, 1 with neovascular glaucoma, and 1 with malignant glaucoma.

Table 2 Breakdown of preoperative therapy and control

Preoperative therapy	Controlled	Not
No therapy	0	5
Topical medication only	7	9
Topical medication + carbonic anhydrase inhibitors	9	29
Total	16	43

SURGICAL PROCEDURE

The majority of operations were performed under general anaesthesia. After a large conjunctival flap had been reflected towards the limbus the superficial scleral flap for trabeculectomy, as described by Watson,⁷ was first prepared. A limbal groove was then extended on each side. 8-0 virgin silk sutures were preplaced in the section and superficial scleral flap prior to excising the deep scleral lamella and completing the section. A peripheral iridectomy was performed adjacent to the trabeculectomy site, followed by cataract extraction and wound closure. A subconjunctival steroid injection was given in 47 out of the 59 eyes.

Results

The immediate and late postoperative complications and the visual outcome have been detailed in Tables 3–6. The control of glaucoma in each diagnostic category has been illustrated in Figs. 1–3. Comparisons of preoperative and postoperative glaucoma control are shown in Tables 7 and 8, and overall glaucoma control is summarised in Table 9

Table 3 Intraoperative complications

Complication	No. of eyes
Capsule rupture	5 (8.5%)
Vitreous loss	2 (3.4%)

Table 4 Immediate postoperative complications

Complication	No. of eyes
Hyphaema	15 (25%)
Ocular hypertension	11 (18.6%)
Flat anterior chamber	4 (6.8%)
Severe uveitis	6 (10.2%)
Iris prolapse	1 (1.7%)
Infection	0

Table 5 Late postoperative complications

Complication	No. of eyes
Retinal detachment	1 (1.7%)
Bullous keratopathy	0
Neovascular glaucoma	1 (1.7%)
Sympathetic ophthalmia	0
Endophthalmitis	0
Phthisis bulbi	3* (5.1%)

*All these eyes had secondary glaucoma.

Table 6 Visual results: preoperative visual acuity compared with that obtained 6 months postoperatively

Total	Diagnostic glaucoma group				
Corr. VA	Preop.	Postop.	Open	Closed	Secondary
6/5–6/12	0%	49%	48%	59%	36%
6/18–6/36	25%	17%	17%	15%	18%
6/60–CF	29%	17%	28%	5%	9%
HM–PL	46%	10%	7%	11%	18%
NPL	0%	7%	0%	10%	18%
Total no of eyes	59	59	29	19	11

VA = visual acuity, CF = counting fingers, HM = hand movements, PL = perception of light, NPL = no perception of light.

(control has been defined as an intraocular pressure of less than 23 mmHg).

ASTIGMATISM

The mean value for the 29 eyes obtaining 6/12 vision or better was 1.96 dioptres. Similar values were obtained for patients with a lower corrected acuity. In no patient was the degree of astigmatism so high as to affect the visual outcome.

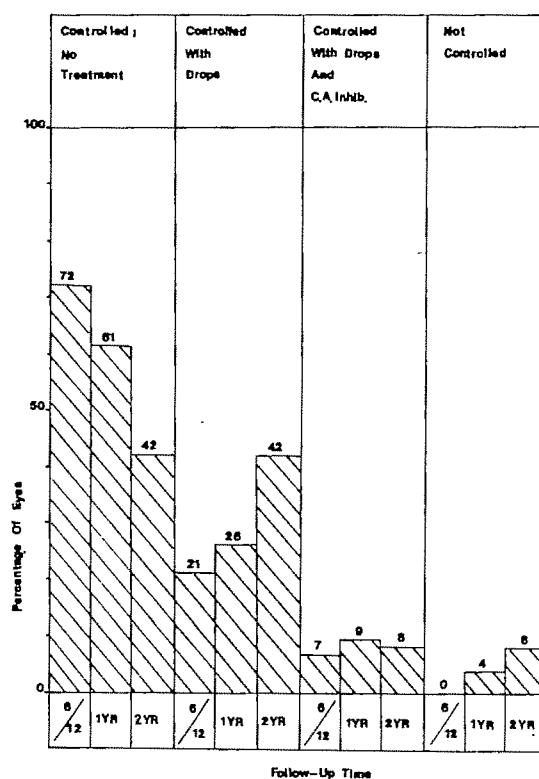


Fig. 1 Primary open-angle glaucoma: control of intraocular pressure after surgery. 29/29 Eyes followed up for 6 months. 23/29 Eyes followed up for 12 months. 14/29 Eyes followed up for 2 years.

Table 7 Overall postoperative glaucoma control for eyes controlled preoperatively

Postop. control	Follow-up		
	6/12	1 yr	2 yr
No treatment	89%	82%	50%
Drops ± CA inhibitor	11%	18%	50%
No control or phthisis	0%	0%	0%
Total no. of eyes	16	11	6

CA = carbonic anhydrase.

Discussion

INTRAOPERATIVE COMPLICATIONS

Two eyes (3.4%) lost vitreous during surgery; one of these eyes had previously had an iridencleisis operation. This rate is in keeping with that expected to complicate an intracapsular extraction (up to 3% quoted by Duke-Elder⁸). Capsule rupture

occurred with 5 eyes (8.5%). Two of these eyes had had previous glaucoma surgery, and all had been on pilocarpine therapy for a long period, resulting in a rigid pupil with posterior synechiae.

IMMEDIATE POSTOPERATIVE COMPLICATIONS

The serious complications of wound dehiscence and

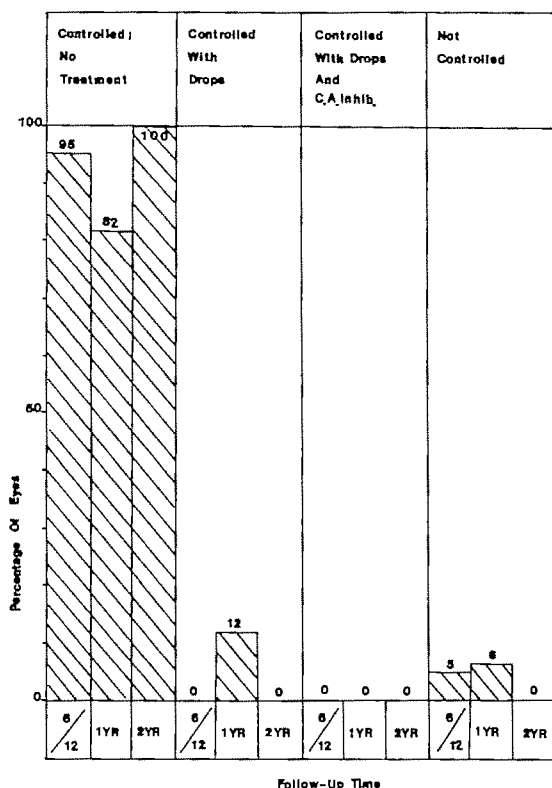


Fig. 2 Primary closed-angle glaucoma: control of intraocular pressure after surgery. 19/19 Eyes followed up for 6 months. 17/19 Eyes followed up for 12 months. 7/19 Eyes followed up for 2 years.

Table 8 Overall postoperative glaucoma control for eyes not controlled preoperatively

Postop. control	Follow-up		
	6/12	1 yr	2 yr
No treatment	71%	55%	54.5%
Drops $\pm$ CA inhibitor	17%	25%	27.5%
No control or phthisis	12%	20%	18%
Total no. of eyes	43	40	22

CA = carbonic anhydrase.

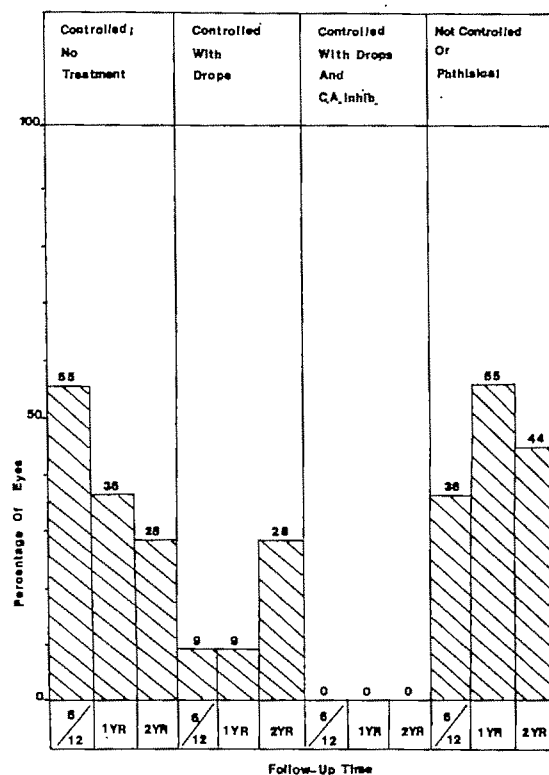


Fig. 3 Secondary glaucoma: control of intraocular pressure after surgery. 11/11 Eyes followed up for 6 months. 11/11 Eyes followed up for 12 months. 7/11 Eyes followed up for 2 years.

Table 9 Overall glaucoma control for all patients

Control	Follow-up		
	6 mths	1 yr	2 yr
No treatment	76.5%	62.5%	53.5%
Drops only	12.0%	17.5%	28.5%
Drops + CA inhibitor	3.5%	4.0%	3.5%
No control	5.0%	10.0%	10.5%
Phthisis	3.5%	6.0%	3.5%
Total no. of eyes	59	51	28

CA = carbonic anhydrase.

infection were absent. A shallow or flat anterior chamber was present at first dressing in 4 eyes (6.8%), associated with a choroidal detachment, but only in 2 cases did it persist more than 3 days. (A flat anterior chamber at 3 days was noted in 3% of trabeculectomies by Ridgway *et al.*).¹ Six eyes had a severe postoperative uveitis, but 4 of these had secondary glaucoma with pre-existing uveitis.

Postoperative ocular hypertension was present in 11 eyes (18.6%), but this settled rapidly in all but 2 cases. The latter both had secondary glaucoma, and in 1 of these an iris prolapse developed.

The 25% incidence of hyphaema was almost double the rate quoted for simple trabeculectomy by Ridgway *et al.*¹ but was consistent with other studies of the combined operation.^{5,6} The hyphaemata all resolved rapidly without complication.

VISUAL RESULTS

Only 29 out of 59 eyes (49%) achieved a corrected visual acuity of 6/12 or better. The main factor accounting for failure to achieve this level of vision was glaucomatous visual damage in 21 out of the 59 eyes (35%). Senile macular degeneration and diabetic maculopathy also contributed.

Apart from those eyes with advanced glaucomatous visual damage 29 out of 38 eyes (76%) achieved 6/12 vision or better; if those eyes with glaucoma secondary to uveitis are also excluded, 25 out of 30 eyes (83%) achieved 6/12 vision or better. These results compare favourably with those obtained in a recent study of intracapsular cataract extraction in nonglaucomatous eyes.⁸

The degree of astigmatism is comparable to that obtained for simple cataract extraction by the limbal approach.

LATE POSTOPERATIVE COMPLICATIONS

Only 1 eye (1.7%) has developed a retinal detachment; bullous keratopathy from endothelial decompensation has not occurred. These results compare favourably with those of routine intracapsular cataract extraction. One patient with chronic angle-closure glaucoma subsequently developed uncontrollable neovascular glaucoma, and 27% of the eyes with secondary glaucoma went on to phthisis bulbi.

GLAUCOMA CONTROL

Overall control of intraocular pressure (less than 23 mmHg) was achieved in 91.5% at 6 months, 84% at 1 year, and 86% at 2 years. These results compare favourably with previous studies of trabeculectomy alone. Ridgway *et al.*¹ quoted 92% controlled in a 3–18 month follow-up, while Wilson³ quoted 85% controlled at 1 year. However, the

proportion of patients requiring additional medical treatment to ensure control of intraocular pressure rose from 15% at 6 months to 21.5% at 1 year and 32% at 2 years. In Wilson's study³ 28.7% required additional therapy at 1 year.

The efficacy of control is related to the diagnostic group and whether the glaucoma was controlled preoperatively or not. Fewer of those patients who were controlled preoperatively required any postoperative medication.

As regards the diagnostic categories, the patients with secondary glaucoma fared conspicuously worse than those with primary glaucoma. Three out of the 11 eyes with secondary glaucoma became phthisical, but 5 were controlled at 1 year, and 4 of the 7 eyes that have been followed up for 2 or more years are still controlled.

The outcome for both chronic open-angle glaucoma and chronic closed-angle glaucoma was excellent; both groups had control rates of over 90% at 1 and 2 years' follow-up. However, more patients with open-angle glaucoma required additional medication to achieve control.

The fact that an increasing percentage of patients require additional therapy to maintain control as the postoperative follow-up extends is very important, and indicates a need for close supervision of these patients. In these 2 groups only 2 eyes required additional therapy between 6 months and 1 year, but subsequently a further 6 eyes required additional medical treatment between 12 and 22 months postoperatively. In a number of these patients glaucomatous visual damage had progressed when failure of control was not detected early. These patients need more frequent follow-up than medically controlled glaucoma patients. This should be at 3-monthly intervals for the first 2 years after surgery.

Conclusions

The combined operation of trabeculectomy and cataract extraction gives results comparable to those obtained for the separate procedures, if allowance is made for the pre-existing glaucomatous visual damage. It is both a safe and effective procedure for patients with cataract and either open- or closed-angle glaucoma. The value of this operation in cataract and secondary glaucoma associated with uveitis is doubtful. The importance of frequent follow-up in the postoperative period has been emphasised.

I thank the consultant surgeons of the Birmingham and Midland Eye Hospital for permission to study their patients, and Miss Eagling for her helpful advice and encouragement.

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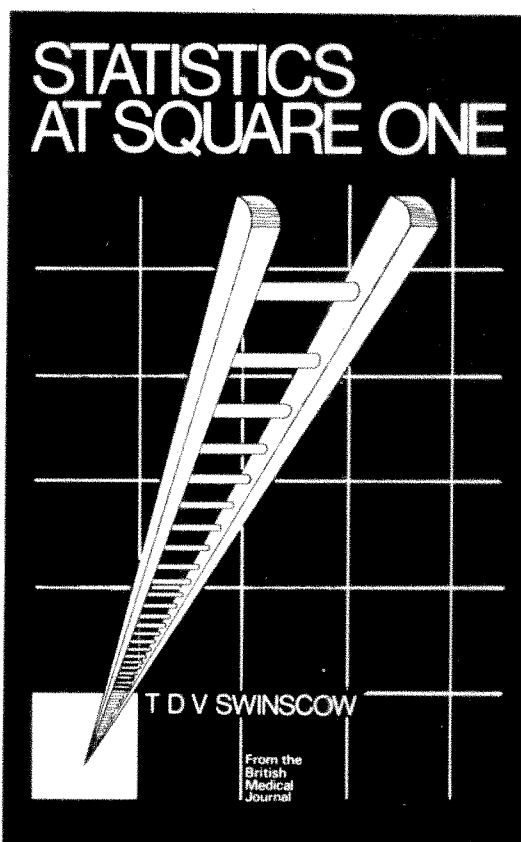
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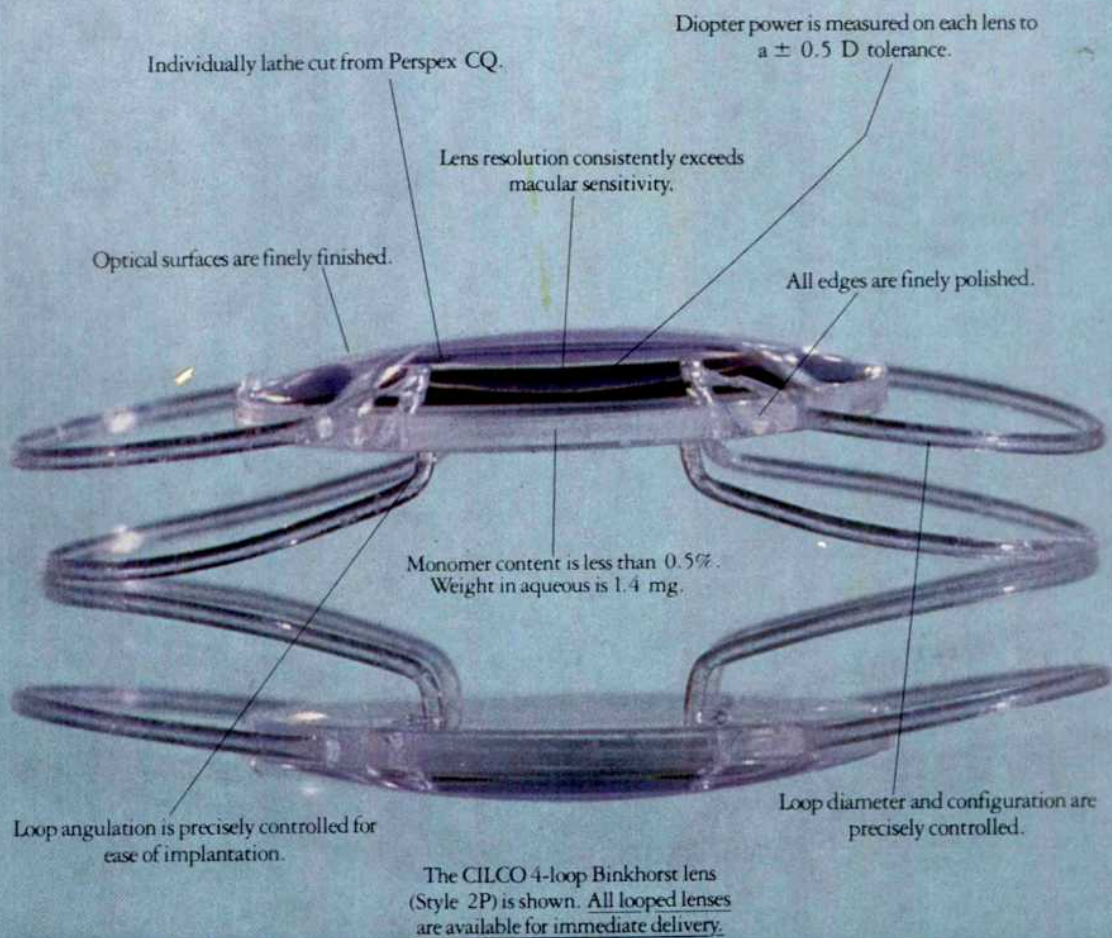
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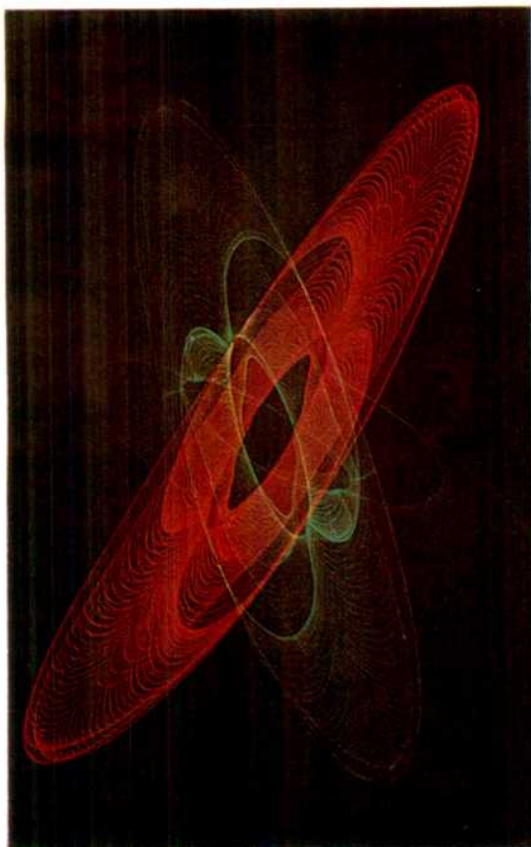
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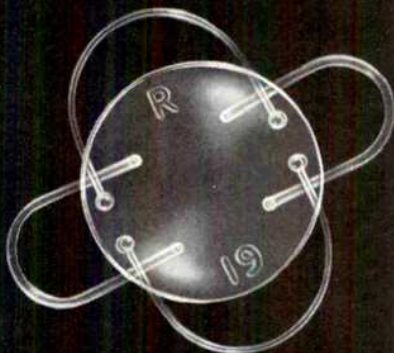
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Editorial: Batten's disease

Batten's disease is a group of rare disorders that present in childhood with retinal and cerebral degeneration and terminate fatally after a prolonged illness. They are inherited as an autosomal recessive condition, with a world wide distribution, and there is as yet no effective treatment. Two cases were described in 1903 by Batten,¹ a physician at the Hospital for Sick Children and the National Hospital for Nervous Diseases, London, though the original description may be attributed to Stengel, who described a Scandinavian family in 1826.² Batten's contribution was to realise that the fundus appearances were different from those of Tay-Sachs's disease, which was described about the same time and later shown to be due to an accumulation of a ganglioside in the brain.³ It soon became apparent that Batten's disease was a group of similar conditions in which autofluorescent material was deposited intracellularly throughout the body and that the various subtypes of the condition could be recognised from its ultrastructural appearances. There is at present no agreement on the composition of this substance, though Zeman and Dyken⁴ postulated that the material was due to the accumulation of ceroid and lipofuscin and suggested Batten's disease should be called neuronal ceroid lipofuscinosis, but recently it has been suggested that vitamin A metabolism might be implicated in the late infantile form.

In this issue of the *BJO* Spalton and colleagues review juvenile Batten's disease. This is the subtype of the disease of most interest to ophthalmologists, since these children present with visual failure. There are about a dozen new cases of Batten's disease a year in Britain, and the juvenile type accounts for a quarter of these. To put this in perspective, there are approximately 100 new blind registrations a year in England and Wales in the 5-15 age group, and since most of these registrations are due to congenital anomalies acquired forms of blindness are unusual. Batten's disease must constitute a significant proportion of children with acquired retinal blindness. Most ophthalmologists will see only an occasional case in the course of a professional career, but early diagnosis of the disease is nonetheless important so that parents can receive genetic counselling and medical advice. There is a 1:4 risk of further children being affected, and there is no method of prenatal diagnosis at present.

The rarity of neurodegenerative diseases presents

a considerable diagnostic challenge and the ophthalmologist should appreciate the significant diagnostic contribution he can make. Careful fundus examination is usually necessary for recognition of the cherry red spot which occurs in Tay-Sachs disease (infantile GM₁, GM₂ types 1 and 2), sialidase deficiency (type 1+2), and acute neuronopathic Niemann-Pick disease (type A). Pigmentary retinopathy may be rarely associated with abeta lipoproteinaemia or Refsum's disease, and recognition of these conditions may have therapeutic implications. Visual loss may also be due to cortical blindness, and adrenoleucodystrophy typically presents in this way. Ocular motor abnormalities may also provide clues, for a vertical supranuclear ophthalmoplegia is often a helpful diagnostic sign of the ophthalmoplegic lipidosis syndrome (with sea blue histocytes), and a horizontal supranuclear ophthalmoplegia may be seen in late onset Gaucher's disease.

Children with visual problems usually have severe visual loss before they come to the ophthalmologist. Some of them will have endocrine or neurological symptoms suggesting a systemic process, but those patients without other signs are the most difficult to deal with. The ophthalmologist must consider compressive lesions (craniopharyngiomas, gliomas), inflammatory conditions (subacute sclerosing panencephalitis), or degenerative disorders. This group with organic disease can usually be separated from children with hysterical blindness by performing a visual evoked response in an experienced department (though hysterical symptoms may mask an underlying organic illness). The variety of further investigations available include neurophysiological procedures, endocrine assays, and computed tomography, and there may be advantages in staff with a special experience with children undertaking them.

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Juvenile Batten's disease: an ophthalmological assessment of 26 patients

D. J. SPALTON, D. S. I. TAYLOR, AND M. D. SANDERS

From the Hospital for Sick Children, Great Ormond Street, and the National Hospital, Queen Square, London

SUMMARY Twenty-six children with juvenile Batten's disease are reviewed. On clinical and histological evidence they appear to represent a specific disease entity, which though rare is a substantial cause of blindness in children aged 5-15 years. Children present with rapid progressive visual loss at age 6-7 years, early mental deterioration, and fits about 2-4 years later, and this is the stage at which the diagnosis is usually made. Macular degeneration appears to be a consistent early feature, and peripheral retinal changes become more marked as the disease progresses. Phototoxicity may possibly play a part in the retinal degeneration.

In 1903 Batten described 2 siblings with progressive macular dystrophy and cerebral degeneration.¹ For many years after this there was a considerable controversy as to whether these 2 conditions were always causally related and whether a macular dystrophy represented a forme fruste of a far more devastating condition. It gradually became established that the 2 conditions were not invariably related, and the group of conditions in which these 2 degenerations occurred together became known as amaurotic familial idiocy. Clinical Tay-Sachs disease was later separated from this group, and the remaining diseases, being characterised by the deposition of autofluorescent pigments in neurones and other cells, became known under the generic name of Batten's disease. Today this group of conditions represents the most common cause of neurodegenerative disease seen in children at the Hospital for Sick Children in London.

Batten's disease can be divided into 4 principal

groups (Table 1) on clinical, electrophysiological, and ultrastructural grounds,²⁻⁴ and although intermediate forms occur it is likely that these groups represent specific disease entities. In the infantile and late infantile types visual loss occurs later in the disease, usually long after the diagnosis has been established. Kuf's disease, or so-called adult Batten's disease, is very rare and certainly does not represent a single disease entity.

Juvenile Batten's disease usually presents with visual failure. It is characterised by early visual loss followed by progressive mental deterioration and fits and is invariably fatal, usually in the early 20s. No treatment has yet been shown to improve the prognosis. The condition is inherited as a recessive trait, and early diagnosis of the disease is important so that genetic counselling can avert the unwanted birth of further affected children. No method of prenatal diagnosis is available.

In the Batten disease complex autofluorescent pigments are deposited especially in neurones, but also in other cells throughout the body, and the ultrastructural examination of these has produced

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Table 1 *Batten's disease: subtypes*

	<i>Old name</i>	<i>Age of onset</i>	<i>Presentation</i>	<i>Electron microscopy</i>
Infantile	Haltia-Santavouri	Infancy	CNS and late optic atrophy	'Snowballs'
Late infantile	Jansky-Bielschowsky	2-4 years		Curvilinear bodies
Juvenile	Spielmeyer-Sjögren	6-8 years	Eyes	Finger-print bodies
Adult	Kuf	Adult	CNS/eyes	?

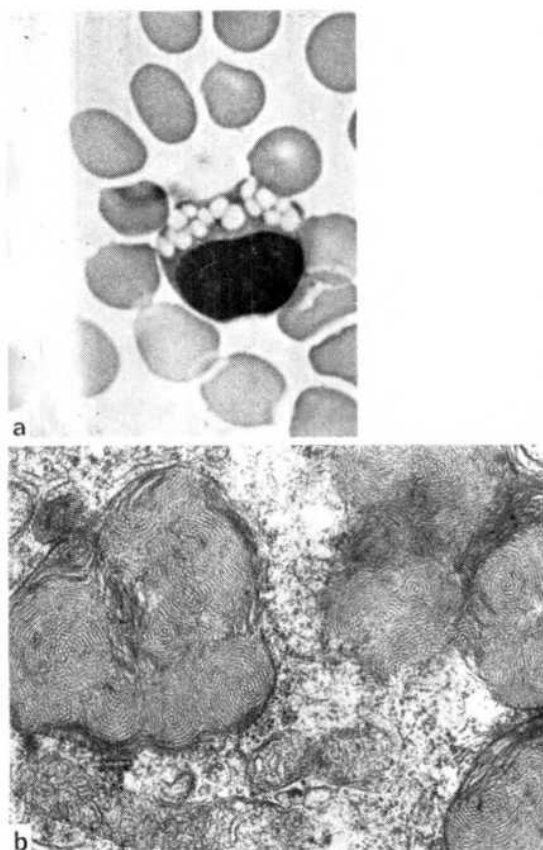


Fig. 1A Vacuolated lymphocyte. About 30% of lymphocytes in the peripheral blood are vacuolated in all children with juvenile Batten's disease. 1B Typical intracellular finger print bodies seen in a rectal neurone of a child with juvenile Batten's disease.

the present classification of the disease.³ Vacuolated lymphocytes are found in the peripheral blood of all patients with the juvenile type, and the deposited intracellular neuronal material has a characteristic ultrastructural 'finger print' form (Figs. 1A and B). The nature of the autofluorescent material is unknown. It has been suggested that the material is ceroid and lipofuscin, pigments normally associated with aging, and the diseases have been called neuronal ceroid lipofuscinoses.⁵ It has been postulated that a defect in peroxidation of fatty acids might be responsible and treatment with antioxidants suggested. The finding of low levels of docosahexaenoic acid in the peripheral leucocytes of 4 patients with juvenile Batten's disease has been used to support this hypothesis.⁶ However, further interest in this group of conditions has been recently stimulated by the sophisticated biochemical analysis⁷

of the brain of a child who died from the late infantile form of the disease which suggested that the stored material was a retinoic acid metabolite. On these grounds a low vitamin A diet has been used to treat some children. Neither antioxidants⁸ nor low vitamin A diets have yet been shown to be convincingly successful treatments. A disease similar to Batten's disease has been found in inbred English Setters and provides a good animal model.⁹

By historical association the Hospital for Sick Children and the National Hospital for Nervous Diseases have always had a special interest in this group of conditions. We have reviewed the ocular findings by histological examination of biopsy material from a group of children diagnosed as having juvenile Batten's disease.

Materials and methods

The case records and fundus photographs of a group of children with juvenile Batten's disease were reviewed. This diagnosis had been confirmed by finding vacuolated lymphocytes in the peripheral blood of all cases and biopsy (usually rectal biopsy) studied by histochemical and electron microscopical techniques in at least 1 member of a family where more than 1 child was affected.

Results

Twenty-six children are included in this series. Five families had 2 affected children, no family had any more than 2. In only 2 families was there a possibility of consanguinity between the parents.

All children, apart from 1 who presented with fits, presented with visual failure (Fig. 2) with a peak incidence of 6 to 7 years of age. Mental symptoms were noticed about the same time or soon afterwards (Fig. 3), and by the time of our review 23 patients had developed fits. These can be accurately dated (Fig. 4), and usually occurred about 2-4 years after the onset of visual failure, though a small number of children did not develop them until much later in the illness. In spite of the presentation with visual failure there was frequently a considerable delay of several years in reaching a definitive diagnosis (Fig. 5), and this was because the diagnosis was not usually established until the onset of fits (Fig. 6). Early diagnosis and genetic counselling would not have prevented the second sibling being affected in any of the 5 families with more than 1 affected child, as in each the second child had already been born by the time the elder sibling had presented.

Nine children had adequate fundus photography and 5 of these also had fluorescein angiograms. Two

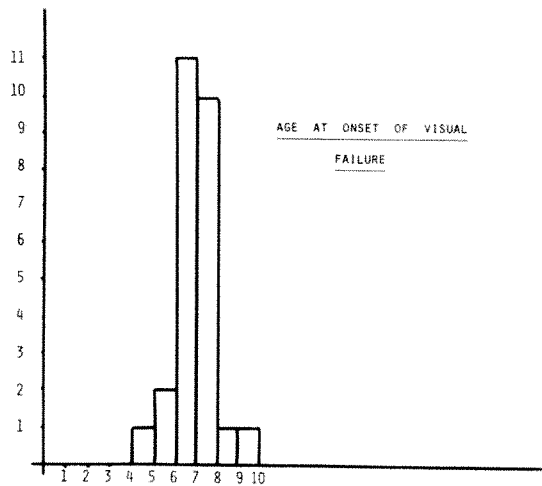


Fig. 2 Children present with visual failure at a peak incidence of 6–7 years of age.

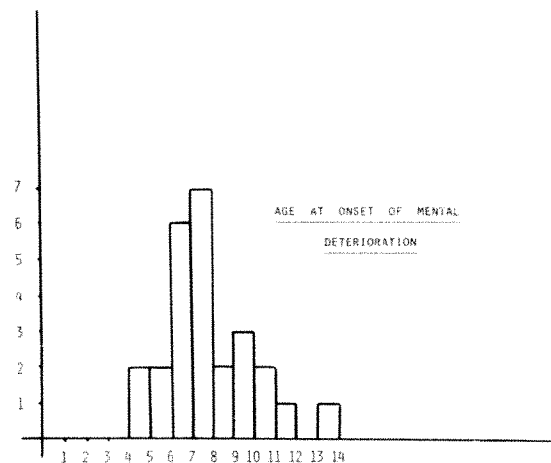


Fig. 3 Mental symptoms are usually apparent at the initial presentation but may be unnoticed.

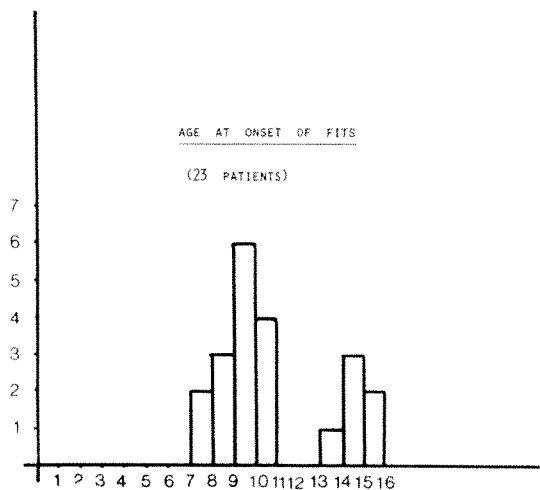


Fig. 4 Fits tend to appear 2–4 years after visual failure.

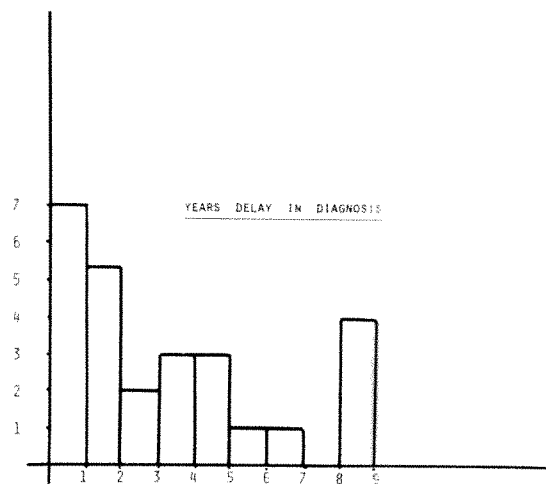


Fig. 5 Diagnosis is frequently delayed for several years.

children showed marked leakage of dye into the retina. The male:female incidence in this series was 11:17.

Discussion

Juvenile Batten's disease is rare. About 2 or 3 new patients are seen each year at the Hospital for Sick Children, and they probably represent the majority of patients seen in England. Nevertheless, in the age range 5–15 years it must be a significant cause of blindness, as approximately 10 children are

registered blind in this age group each year in England from retinitis pigmentosa, macular lesions, or other retinal disease which might be included in the differential diagnosis of juvenile Batten's disease.¹⁰

All the children presented with visual failure (apart from 1 child who developed fits a few months previously) with a peak incidence at 6–7 years of age (Fig. 2). Typically juvenile Batten's disease produces a bull's eye macular dystrophy (Figs. 7A and B), but while a review of the available fundus photographs (from 9 patients) showed pigmentary

macular changes in each case these were frequently subtle and easily missed unless the pupils were dilated and the fundus examined carefully (Fig. 8). Fluorescein angiography defined the pigmentary disturbances much more clearly (Figs. 9A and B), and in our patients, although they were not all fully documented photographically, it is unlikely that the disease occurs in the presence of a normal macula. Two patients showed leakage of fluorescein from the retinal circulation (Figs. 9B, 10A, and B) and it is probable that this is a sign of an actively degenerating retina, as it is seen in a variety of other tapetoretinal degenerations.¹¹ About half the

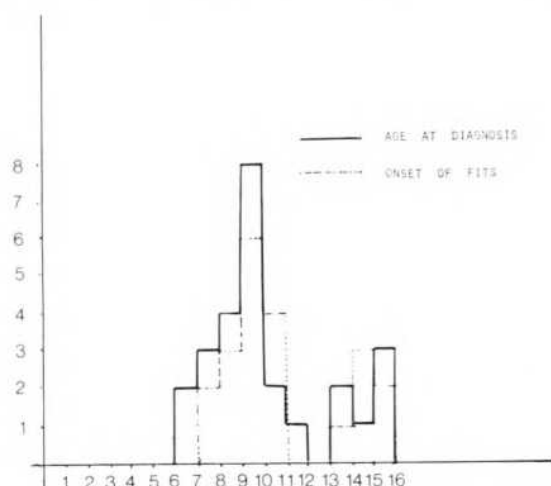


Fig. 6 Definitive diagnosis is usually made at the onset of fits.

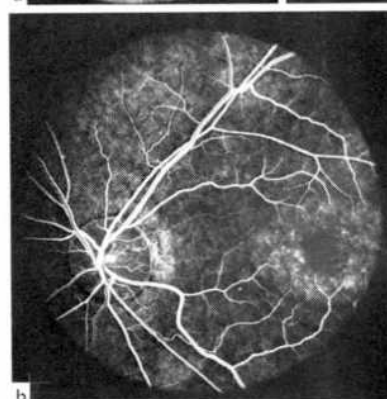
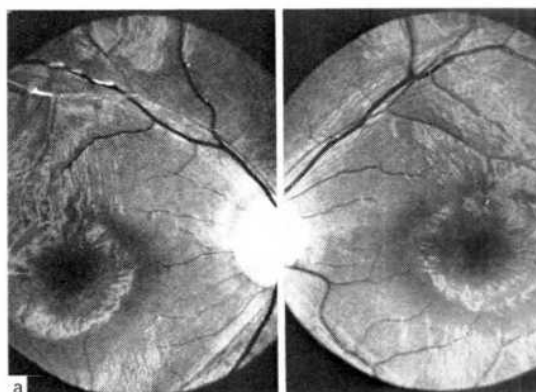


Fig. 7A The posterior poles of an 8-year-old girl. There is a typical bull's eye maculopathy, thinning of the retinal arterioles, and optic disc pallor. 7B The fluorescein angiogram of the left eye showing the pigment epithelial disturbances.

Fig. 8 Subtle macular pigmentation in each eye of a 7-year-old girl.



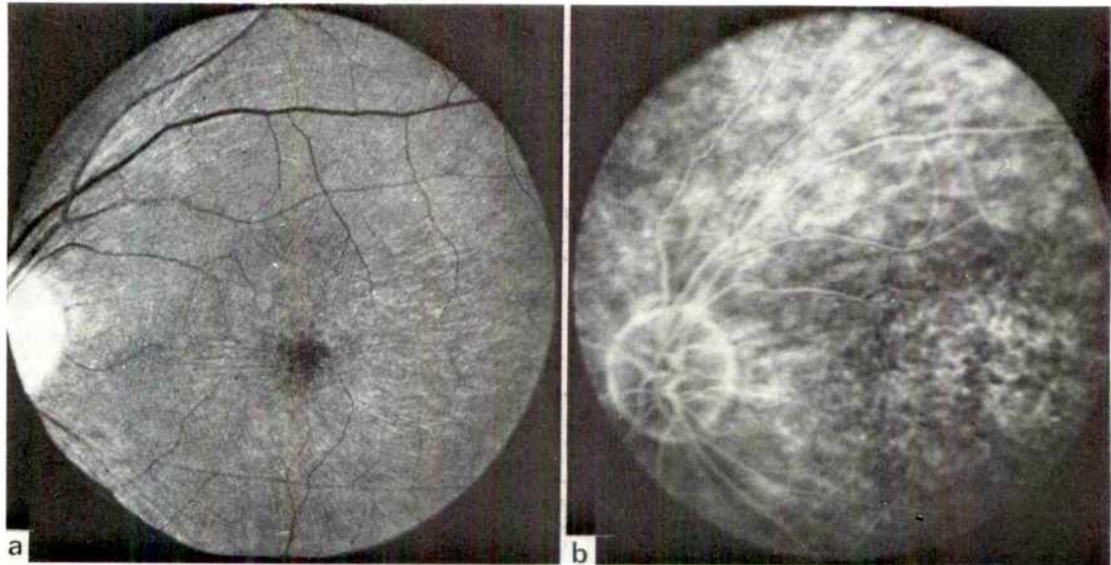


Fig. 9A The posterior pole of a 9-year-old child. 9B Fluorescein angiography emphasises the pigmentary disturbance and shows leakage of dye from intraretinal vessels.

patients were initially diagnosed as tapetoretinal degeneration. The peripheral retina in our patients varied from a normal appearance to pigment epithelial atrophy or peripheral pigmentation (Fig. 11), and this is probably related to the age of the patient and the clinical stage of the degeneration. Bone corpuscular pigment occurred very late in the course of the disease (Fig. 12).

Young children with visual loss of whatever cause do not tend to complain of this until it is severe, and the children in this series were no exception, often being referred for ophthalmic opinion only when their visual loss was so severe that they bumped into things or were having visual difficulties at school. The visual failure tended to have a fairly rapid course, with the child being registered blind within 1 to 2 years of developing symptoms. By the time the children present it is likely that there has already been considerable structural retinal damage, and at this stage it is unlikely that any treatment would restore vision.

It is always difficult to gauge the onset of loss of skills or mental retardation, but frequently these were apparent, though perhaps not recognised, when the child presented with visual loss (Fig. 3), and this correlates with the animal model.⁹ Many children seem never to have been really bright, lagging behind their unaffected siblings in their achievement of early milestones and several had already been labelled dull or educationally sub-normal before their visual loss. One child also had

Down's syndrome. Retrospectively more easily recognisable symptoms occurring at the time of visual loss were loss of recent memory, tantrums, speech disturbances or poor learning ability at school, but these symptoms were often overlooked in the turmoil of visual failure.

The onset of fits can be accurately documented (Fig. 4). They tend to occur 2–4 years after presentation, with a small group of children developing them later in their teens. Although it is possible that they represent a subgroup in the disease, this is unlikely, as 1 of these children who developed fits when aged 15 had a brother who developed fits at the age of 9. The severity of fits varied; sometimes they presented a major therapeutic problem but occasionally were not troublesome until late in the illness.

Visual loss in dull children is a major diagnostic problem and it was sometimes many years before the final diagnosis was made (Fig. 5). Most children were referred with a diagnosis of tapetoretinal degeneration, retinitis pigmentosa, or macular dystrophy, but a few unfortunate children were inevitably thought to be hysterical and subjected to prolonged investigation through the social services before the development of more overtly organic symptoms stimulated reappraisal. In the absence of another affected sibling the diagnosis was usually made at the onset of fits (Fig. 6). In young children presenting with a tapetoretinal problem the ophthalmologist must take a careful history, and if there is

any suggestion of mental deterioration further investigations are necessary. The electroencephalograph provides good evidence of underlying cerebral dysfunction,⁴ and suspicious abnormalities indicate the need to search for vacuolated lymphocytes in the peripheral blood and the confirmation of the diagnosis by suction rectal biopsy. Although it is possible to diagnose the condition by blood examination in apparently normal younger siblings, many parents do not wish this, preferring to await the course of events.

Seven of the 26 children were noted to hold their eyes in a raised position, apparently 'overlooking' the target (Figs. 13A and B). The reason for this is

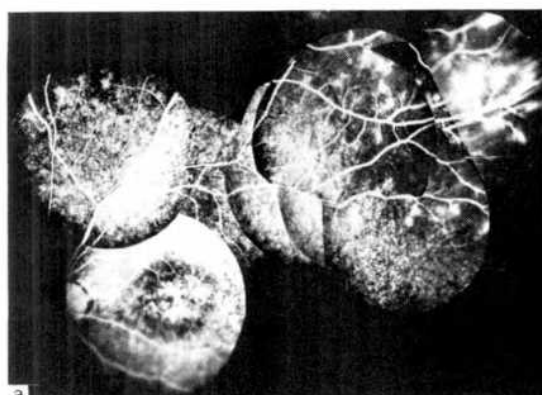


Fig. 10A Fluorescein angiography at age 5 shows leakage from peripheral retinal vessels. 10B One year later there is extensive leakage of dye throughout the retina. This is probably a sign of active retinal degeneration (patient of Professor A. C. Bird).

unknown, but it might be explained by increased phototoxicity of their retinæ. Phototoxicity has been well established in animals reared under constant illumination¹² and light has been shown to be detrimental to the retina of the RCS rat.¹³ Most of the natural retinal illumination comes from above and, if the retina was especially sensitive to light,

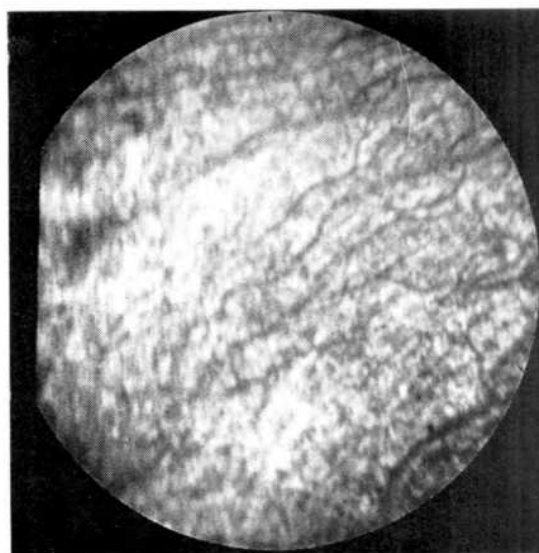


Fig. 11 Pigment epithelial atrophy in the peripheral retina of a 7-year-old boy.

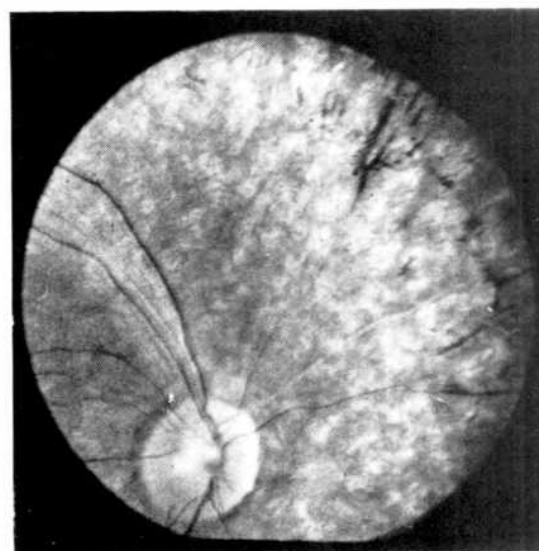


Fig. 12 Peripheral intraretinal bone corpuscular pigmentation in the retina of a 15-year-old girl. This occurs late in the disease.



Figs. 13A, 13B 'Overlooking' in 2 children. These 2 children were both asked to look straight at the camera and to fixate appeared to have to 'overlook' the target. This sign was seen in 7 of the 26 children.

might be expected to destroy preferentially the inferior retina, leading the child to fixate with the relatively unaffected superior retina and overlook the target. Experimentally phototoxicity affects the outer retina initially,¹⁴ and this has similarities with the retinal histology of juvenile Batten's disease, in which the outer retina is affected earliest.¹⁵ It is interesting to speculate whether phototoxicity might be a factor in determining the fundus appearances. Studies of albino rats reared in constant illumination showed that the posterior pole was more susceptible and that rods were more affected than cones,¹⁶ although experiments with pigeons under rather different conditions suggested that cones were the more susceptible to light.¹⁷ If this hypothesis is true visual deterioration might be simply delayed by giving the child dark glasses to wear or occluding the eye.

We thank Dr Edward Brett and Dr Rosemary Stephens for letting us see their patients and Dr Ann Harden and Dr Brian Lake for their help and advice.

Miss Josephine Lace typed the manuscript and Mr Rolf Sennhenn produced the photographs.

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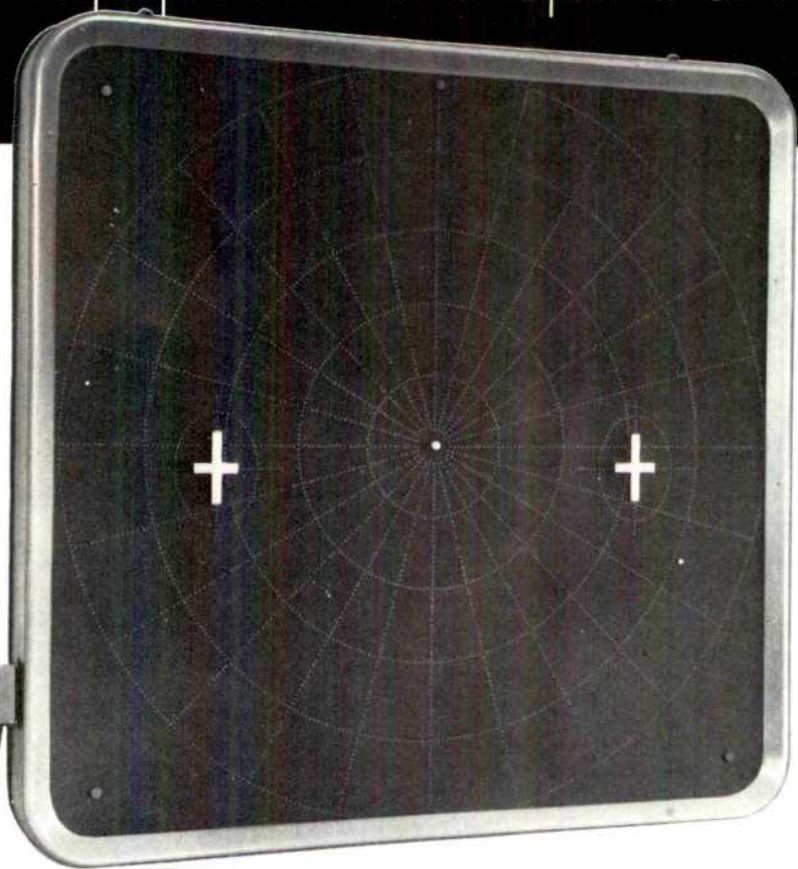
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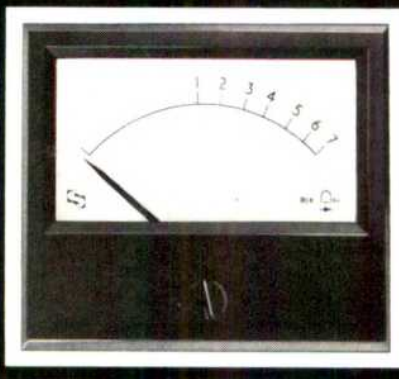
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Adult vitelliform macular degeneration: diagnosis and natural history*

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SUMMARY True vitelliform dystrophy rarely appears in the adult population. We describe 10 cases in adults of bilateral vitelliform lesions clinically mistaken for Best's disease. Fluorescein angiography is a useful tool in distinguishing this dystrophy from Best's disease or other diseases. The angiographic findings suggest pigment epithelial disease. Adult vitelliform degeneration may lead to dry atrophic macular degeneration in a similar fashion as macular drusen. Symptoms and visual findings in these patients are fairly stable, and may be only slowly progressive in spite of ophthalmoscopic and fluorescein angiographic changes over a period of years. The electro-oculogram is useful in separating adult vitelliform macular degeneration from true vitelliform dystrophy.

For the past 70 years the 'poached egg' appearance of the macular lesion in vitelliform macular dystrophy has been described in various ways. The example presented by Best in 1905 has become the standard and since has been known as Best's disease.¹ Other descriptive terms are vitelliform,² vitelliruptive macular degeneration,³ vitelline macular degeneration,⁴ vitelliform dystrophy of the fovea,^{5,6} and inherited macular cyst.⁷

The classic presentation of the disease is a bilateral and symmetrical maculopathy with an autosomal dominant mode of inheritance.^{6,8} The vitelliform lesion typically measures $\frac{1}{2}$ to 3 disc diameters, and usually presents before the second decade of life. Visual acuity is frequently normal but may be minimally decreased in the vitelliform stage of Best's disease. A mild red-green dyschromatopsia is seen in later stages of the disease.

Fluorescein angiography typically shows hypofluorescence in the area corresponding to the vitelliform lesion in Best's disease.^{9,10} The electro-oculogram (EOG) findings are pathologically subnormal. Deutman demonstrated subnormal EOGs in family members of patients with proved Best's disease, suggesting detection of a carrier state.^{5,6}

Vitelliform macular dystrophy is believed to be a disease of retinal pigment epithelium.^{6,8} The intact

vitelliform lesion ultimately leads to chorioretinal atrophy, with the terms 'scrambled egg' and 'pseudohypopyon' employed to describe stages in the natural progression of Best's disease.

Gass^{11,12} described 9 cases of what he termed 'peculiar foveolar macular dystrophy'. His patients had bilateral, symmetrical, slightly raised yellow subretinal lesions that were $\frac{1}{3}$ disc diameter with a central pigment spot. The onset of the disease was primarily in the 30 to 50 year age group, with symptoms of blurred vision and metamorphopsia. There was a slow progression of visual loss in these patients. Gass found normal to slightly abnormal EOG readings in these cases. Fluorescein angiography showed either a hypofluorescent lesion or, more typically, a small ring of hyperfluorescence surrounding a hypofluorescent foveolar spot. Pathological changes were noted in the retinal pigment epithelium, and there was some question of the relationship of this entity to familial drusen.

In 1977 Fishman *et al.* described 3 patients with bilateral vitelliform-like lesions who had normal EOG findings.¹³ These authors used the term 'pseudovitelliform macular degeneration' to describe the condition. These patients were all older than 45 years of age and had a visual acuity of 20/100 or better. Fluorescein angiography showed hyperfluorescence surrounding the foveolar region, and they considered this was due to leakage from the perifoveolar capillaries. The authors emphasised the use of EOG in differentiating pseudovitelliform degeneration from Best's disease.

Kingham and Loeber described 6 cases of vitelli-

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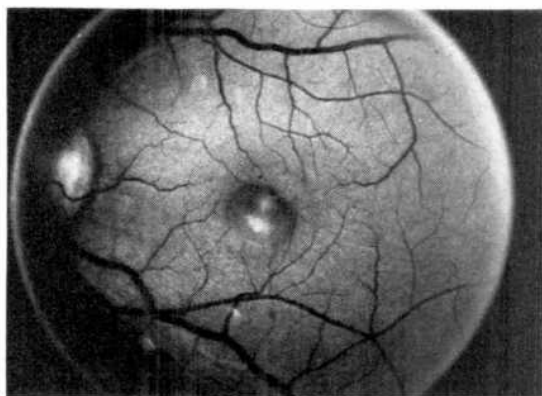


Fig. 1 (Case 1) Left macula with vitelliform-like lesion.

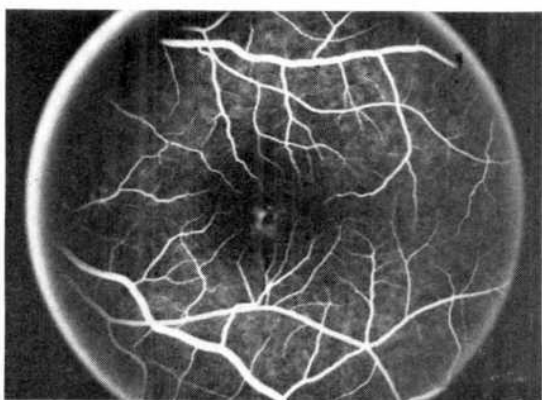


Fig. 2 (Case 1) Late venous phase angiogram of left eye showing ring hyperfluorescence with minimal subretinal leakage in macular region.

form macular degeneration with normal EOGs.¹⁴ Angiography in their cases revealed hyperfluorescence due to pigment epithelial changes. Leakage in the late stages was thought to arise from the choroid and not the perifoveal capillary network.

We investigated 10 cases of adult vitelliform lesions. When initially seen, the diagnosis of vitelliform macular dystrophy was considered. However, the age of presentation and the results of the retinal function tests ruled out Best's disease. Emphasis is directed to the diagnosis and natural history of adult vitelliform macular degeneration.

Case reports

CASE 1

A 45-year-old black female complained of a gradual progression of blurring vision and metamorphopsia in the left eye for 3 years. There was no history of previous medical or ocular disease or ocular trauma.

Physical examination revealed 20/30 vision bilaterally with her present correction of a +0.50 sphere in each eye. However, a +1.25 sphere improved the acuity to 20/25+ in the right eye and a +1.00 sphere +0.50 cylinder axis 90° resulted in 20/25+ vision in the left. The anterior segments, pupils, extraocular movements, and intraocular pressures were within normal limits. Amsler grid, Goldmann perimetry, and colour vision testing gave normal results. Fundus examination disclosed normal-appearing optic discs. However, in both macular regions there were $\frac{1}{2}$ disc diameter, slightly raised, vitelliform-like lesions (Fig. 1).

Fluorescein angiography showed early hyperfluorescence in the macular region in a ring-like fashion in a window defect pattern OU. Minimal subretinal leakage of dye was seen bilaterally in late stages of the angiogram (Fig. 2). The EOG was 2.1 in the right eye and 1.7 in the left eye. Examination of 6 family members failed to disclose any retinal or macular disease. Evaluation of the patient 1 year later revealed no change in ocular symptoms. The best visual acuity was 20/25+ OU, but her refraction changed to +0.50 sphere in the right eye and +0.50 sphere +0.25 cylinder axis 90° in the left. Amsler grid, colour vision tests, and visual fields were unchanged.

In both macular regions the vitelliform lesions had evolved into flat 'scrambled' lesions secondary to retinal pigment epithelial changes (Fig. 3). The fluorescein angiogram showed hyperfluorescence in a window defect pattern in both eyes.

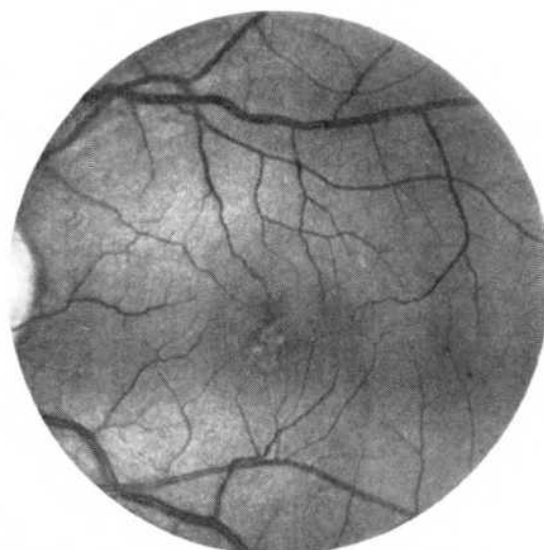


Fig. 3 (Case 1) Left macular region 1 year later. Notice scrambling of vitelliform lesion.

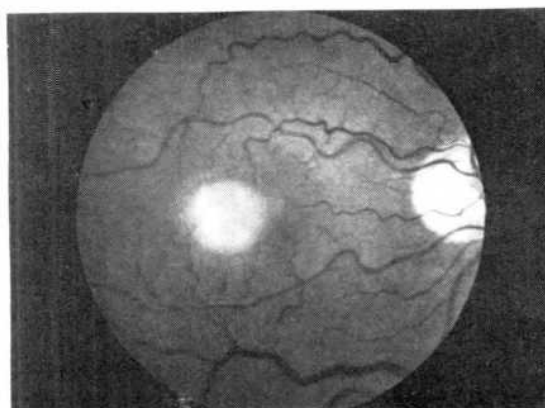


Fig. 4 (Case 2) Right macular region with $\frac{1}{2}$ to $\frac{3}{4}$ disc diameter raised adult vitelliform lesion (1974).

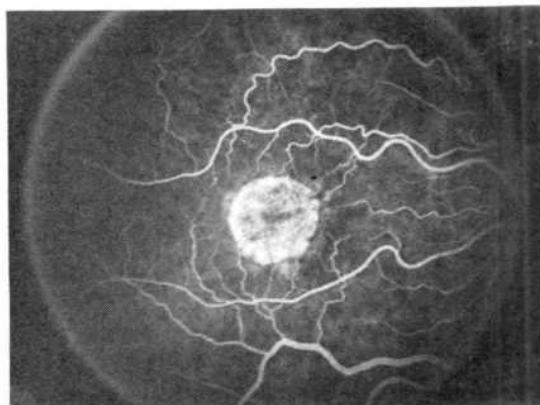


Fig. 5 (Case 2) Late venous angiogram right eye with central areolar choroidal sclerosis pattern (1978).

CASE 2

A 76-year-old white male complained of a gradual decrease of vision in both eyes, primarily at near vision, for the past 5 years. This patient was first described by Fishman *et al.* in 1977.¹³ The patient denied any history of metamorphopsia, photopsia, photophobia, or previous ocular problems. He had cardiac arrhythmias that were being treated with a pacemaker. Visual acuity was best corrected to 20/400 OU and Jaeger 10 in the right eye and Jaeger 8 in the left. There were 2+ anterior cortical, and 2+ nuclear sclerotic changes in both lenses, accounting for some loss of vision. Intraocular pressures, pupils, and extraocular movements were within normal limits. Amsler grid studies showed small areas of distortion in the inferotemporal quadrant in the right eye and in the superonasal quadrant in the left eye. Colour vision tested by isochromatic plates showed a red-green colour deficiency in both eyes. When the patient was seen in 1974, fundusoscopic examination revealed vitelliform-like lesions in both eyes that were approximately $\frac{1}{2}$ to $\frac{3}{4}$ disc diameters in size (Fig. 4). In addition, a 1 disc diameter pigmented naevus was noted superior to the left macula in 1974. Fluorescein angiography showed late subretinal leakage of dye in both eyes. An EOG in 1977 showed a value of 1.86 in the right eye and 2.08 in the left eye.

In 1978 ophthalmoscopic examination disclosed hyperpigmentation of the left foveal region at the level of the retinal pigment epithelium. Surrounding this was a ring of hypopigmentation. The naevus was unchanged. The right eye had an appearance of central areolar choroidal sclerosis (Fig. 5).

Angiographic study revealed ring-like hyperfluorescence in a window defect pattern surrounding central hypofluorescence in the left macular region.

In the right eye early hyperfluorescence and a discrete circular pattern of central areolar choroidal sclerosis was noted (Fig. 4). There was no leakage or pooling of dye in either eye. Electrical studies were not permitted at this time in view of the patient's medical condition. Examination of the patient's 2 children failed to disclose any retinal or macular pathology.

CASE 3

A 70-year-old white female gave a 7- to 8-year history of progressive and gradual decrease of vision in both eyes. She denied other ocular symptoms, previous eye disease, or eye trauma. Pertinent medical history included hypertension medically controlled with a diuretic.

Ocular examination revealed a best corrected vision of 20/200 and 20/60 in the right and left eye, respectively. Near visions were Jaeger 8 in the right eye and Jaeger 3 in the left. The anterior segments were normal, except for 1+ nuclear sclerotic changes in both eyes. Applanation tonometry was within normal limits. Amsler grid showed superotemporal and inferonasal areas of distortion in the right eye. The Amsler grid in the left eye was within normal limits.

Fundus examination from July 1975 revealed a $\frac{1}{3}$ disc diameter vitelliform-like lesion that involved both macular regions. Fluorescein angiography in 1975 disclosed a ring of early hyperfluorescence in both macular regions. Late photographs demonstrated minimal subretinal leakage of dye.

Ophthalmoscopic examination in May 1978 revealed bilateral normal appearing optic discs. In the right macula a $\frac{1}{2}$ disc diameter vitelliform-like lesion was seen and appeared larger. A similar $\frac{1}{3}$ disc diameter lesion with a central pigment spot was

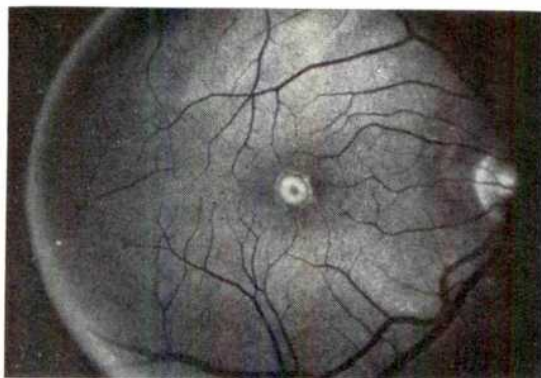


Fig. 6 (Case 4) Right eye showing umbilicated vitelliform lesion with central hyperpigmentation.

noted in the left eye. No other retinal or choroidal pathology was noted. Fluorescein angiography in 1978 showed an increase in the central hypofluorescence in the right macular region when compared with the 1975 study. However, a ring of early hyperfluorescence surrounding the fovea persisted, and late photographs showed minimal subretinal leakage of dye. Angiography of the left eye showed hyperfluorescence in the macular region in a window defect pattern with no leakage detected, consistent with dry atrophic macular degeneration. An EOG was not permitted. Examination of the patient's son did not disclose macular pathology.

CASE 4

A 63-year-old white male noted blurring of vision, and metamorphopsia in both eyes for the past 2 years. He denied previous medical or ocular problems and there was no history of ocular trauma. He was referred to our fluorescein angiography laboratory in August 1977, and visual acuity was 20/30 OU at that time. Ophthalmoscopically, $\frac{1}{4}$ disc diameter umbilicated vitelliform-like lesions were noted in both eyes (Fig. 6). Angiography revealed early hyperfluorescence in a ring-like configuration, which persisted as a window defect.

Examination in 1978 showed a best corrected visual acuity of 20/30+ in both eyes. The anterior segments, extraocular movements, pupils, and intraocular pressures were within normal limits. Amsler grid testing revealed distortion of the central 4 squares in both eyes. Colour vision and visual field testing failed to disclose any abnormalities. The ophthalmoscopic and fluorescein examination had not changed from the study done 1 year previously. Examination of 2 family members did not reveal macular disease. Electrical studies were not permitted.

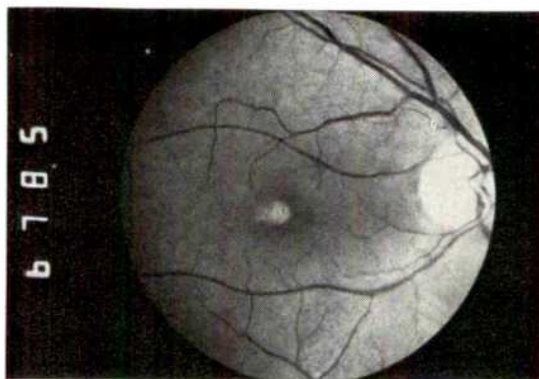


Fig. 7 (Case 6) Right eye with small raised vitelliform lesion.

CASE 5

A 78-year-old white female gave a 6-month history of blurred vision in both eyes. She denied other ocular symptoms or previous eye disease. Best corrected visual acuity was 20/50 bilaterally. The external and anterior segment examinations of both eyes were normal. Ophthalmoscopy disclosed normal optic disc, but $\frac{1}{3}$ disc diameter vitelliform-like lesions were noted in both macular regions. Perimacular drusen were seen bilaterally. Fluorescein angiography showed minimal late leakage of dye beneath the sensory retina in both macular regions, more noticeable in the left eye. The EOG was 2.22 in the right eye and 2.40 in the left.

CASE 6

A 70-year-old white female had a 6-month history blurred vision in both eyes. She denied other ocular symptoms or previous eye disease. Medical problems were denied. Best corrected visual acuity was 20/30 in the right eye and 20/40 in the left eye. Anterior segments, pupils, extraocular movements, and intraocular pressures were unremarkable bilaterally.

Fundus examination revealed vitelliform-like lesion in both macular regions (Fig. 7). No evidence of peripheral retinal disease was noted. Fluorescein angiography showed early hyperfluorescence in the macular regions which persisted as a window defect suggestive of retinal pigment epithelial changes. The EOG was within normal limits bilaterally (2.19 OD, 2.58 OS).

CASE 7

A 43-year-old white female described blurred vision in both eyes since 1961. She was given glasses at that time, with resultant visual improvement. In 1974 she had a decline in vision with metamorphop-

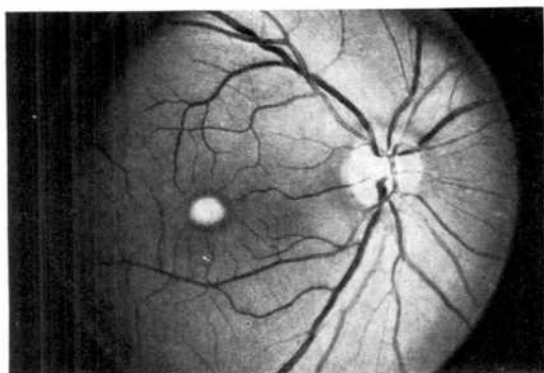


Fig. 8 (Case 7) Right eye with $\frac{1}{4}$ to 1.3 raised adult vitelliform lesion (1974).

sia in both eyes, the right eye being worse than the left. Best corrected visual acuity at that time was 20/40 in the right eye and 20/25 in the left eye. Ophthalmoscopic examination in 1974 revealed bilateral macular vitelliform-like lesions (Fig. 8). Angiography revealed a faint ring of hyperfluorescence in the foveolar region. In 1975 electrical studies were normal, and the patient was told that she did not have Best's disease.

In 1977 she had recurrent, blurred vision. Examination at another institution revealed vision acuities of 20/50 in the right eye with a +2.00 sphere and 20/30 in the left eye with a +1.75 sphere. The remainder of the ocular examination was within normal limits. Electro-oculograms at that time revealed a light peak to dark trough ratio of 1.37 in the right eye and 1.66 in the left eye. On the basis of the EOG findings her condition was diagnosed as hereditary vitelliform macular degeneration.

In March 1978 the patient had a persistent

decrease in visual acuity with metamorphopsia, primarily in the right eye. There were no medical problems or any use of medications. Her mother and sister also had a history of ocular problems. The patient's visual acuity was correctable to 20/40, Jaeger 3 with a +2.75 sphere +0.50 cylinder axis 70° in the right eye, and 20/30, Jaeger 1 with a +1.75 sphere in the left. The Amsler grid showed distortion of the central 4 squares in the right eye. However, no visual field defect could be detected by Goldmann perimetry. Amsler grid and visual fields were normal in the left eye. Colour vision studies were normal bilaterally.

Ophthalmoscopically, bilateral normal optic discs were seen. However, in each macular region there was an approximate $\frac{1}{3}$ disc diameter vitelliform-like lesion. In the right foveolar region there was a small focal area of central hyperpigmentation at the level of the retinal pigment epithelium that was not seen ophthalmoscopically in 1974 (Fig. 9).

Fluorescein angiography revealed more hyperfluorescence, which persisted as a window-defect pattern in both eyes when compared with the 1974 angiogram (Fig. 10). There was no evidence of leakage or pooling of fluorescein. Repeated electrical studies were performed. The EOG was normal in the left eye (1.85) and borderline low in the right eye (1.66).

CASE 8

A 63-year-old white female, mother of case 7, gave a history of blurred vision and poor night vision in both eyes since age 45, the right eye being worse than the left. The symptoms had been stable for the past 3 to 4 years. Previous medical problems included Hashimoto's disease, which was treated medically with levothyroxine sodium 0.1 mg/day. She



Fig. 9 (Case 7) Right eye 4½ years later showing an increase in central hyperpigmentation of the macular lesion (1978).

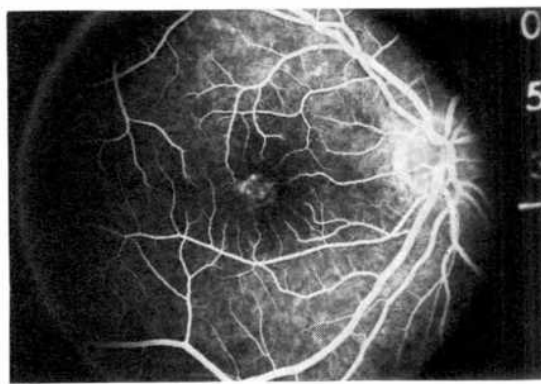


Fig. 10 (Case 7) Midvenous phase fluorescein angiogram with multiple RPE window defects in right macula. There was no leakage present in later photographs (1978).

denied previous ocular disease or history of eye trauma.

The ocular examination revealed a best corrected vision of 20/80, Jaeger 4 in the right eye, and 20/40, Jaeger 2 in the left eye. Anterior segments, extraocular movements, pupils, and intraocular pressures were all within normal limits. Colour vision by isochromatic colour plates was normal bilaterally. Amsler grid studies showed distortion of the central 4 squares in the right eye. However, no field loss could be detected by Goldmann perimetry. Ophthalmoscopy revealed a $\frac{1}{2}$ to $\frac{1}{3}$ disc diameter, slightly elevated, vitelliform-like lesion in the right eye. The left eye appeared more consistent with a dry atrophic macular degenerative process.

Fluorescein angiography of the right eye disclosed an early hyperfluorescent ring type window defect in the macular region. Fluorescein angiography of the lesion in the left posterior pole revealed a similar window defect type of hyperfluorescence. The EOG was normal bilaterally, with light to dark trough ratios of 2.01 in the right eye and 1.90 in the left eye.

CASE 9

A 78-year-old woman had a gradual onset of blurred vision and distortion in both eyes since 1969. She had no refractive change or decrease in her visual status for the past 2 years. Ocular trauma or previous ocular disease was denied. Her medical problems included hypertension, atherosclerotic cardiovascular disease, and thyroid problems. Her medications included digoxin and a diuretic.

Visual acuity was 20/80 Jaeger 3 in the right eye, and 20/60, Jaeger 3 in the left eye. Pupils, extraocular movements, and intraocular pressures were all within normal limits. The lens showed early nuclear sclerotic changes in both eyes. Amsler grid, visual

field, and colour vision were within normal limits bilaterally.

Examination of the 1975 photographs revealed bilateral $\frac{1}{3}$ disc diameter, vitelliform-like lesions in both eyes (Fig. 11). There was also diffuse retinal pigment epithelial thinning that exposed the underlying choroidal vasculature. Multiple punctate hypopigmented lesions at the level of the retinal pigment epithelium were seen in the left eye that were suggestive of drusen.

Fluorescein angiography in 1975 showed early hyperfluorescence in a doughnut type fashion that involved both macular regions. In addition small punctate lesions fluoresced in the midvenous phase, consistent with typical drusen. In the late angiographic stage there was a persistent window-defect type of hyperfluorescence in the macular region, with no evidence of pooling or leakage of dye.

Ophthalmoscopic examination in 1978 revealed multiple drusen-like changes in the left macular region that resembled atrophic macular degeneration. However, in the right eye, there was increased pigmentation in the macular region quite different from that in 1975 (Fig. 12). Fluorescein angiography similarly revealed early hyperfluorescence of both macular areas with evidence of perimacular drusen. Late fluorescein angiography revealed a ring-type window defect involving the right macular region. A similar pattern was seen in the left eye. No evidence of pooling or leakage could be seen. Electrical studies were not permitted.

CASE 10

A 63-year-old black female complained of blurred vision in both eyes since 1972. She denied previous ocular or medical disease, and family history was negative. Best corrected visual acuity was 20/30, Jaeger 2 in each eye. The anterior segments, pupils,

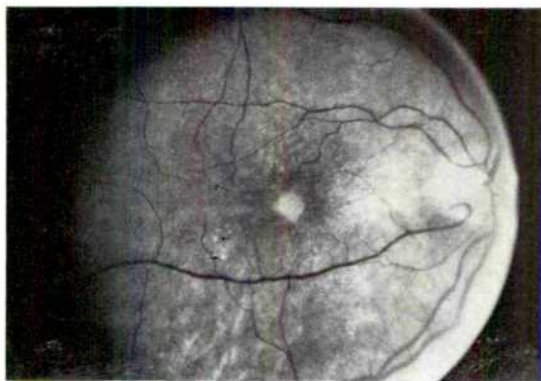


Fig. 11 (Case 9) Right eye adult vitelliform lesion in macula. Drusen are also present (1975).

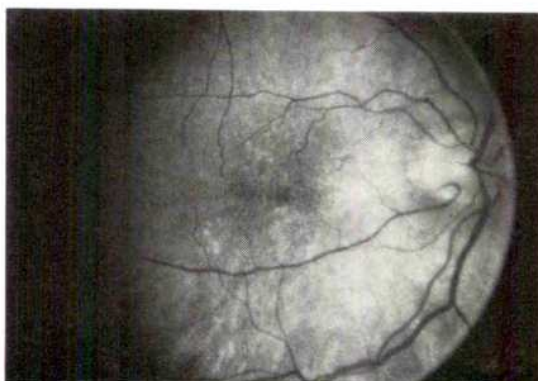


Fig. 12 (Case 9) 3 years later the vitelliform lesion has disappeared. Angiography was compatible with dry atrophic macular degeneration.

extraocular movements, and intraocular pressures were normal bilaterally. Amsler grid, colour vision, and visual fields were normal in each eye. Ophthalmoscopy revealed bilateral, 1/3 disc diameter vitelliform-like lesions. In addition there were scattered paracentral drusen. Angiography revealed hyperfluorescence in a window defect pattern similar to that seen in dry atrophic macular degeneration. Electrical studies were not permitted.

Discussion

The differential diagnosis of vitelliform or egg yolk lesions should include central serous choroidopathy, Best's disease, inflammatory aetiology (toxoplasmosis), retinal pigment epithelial detachment, macular drusen, and other macular degenerations (pseudovitelliform and peculiar foveal macular dystrophy). Our 10 patients were unusual in that the vitelliform-like lesions were atypical of Best's disease: (1) The lesions were smaller in size and with greater asymmetry. (2) Angiographically they did not block fluorescence. (3) The lesions occurred in an adult population. (4) EOG findings were normal. (5) The natural history differs.

Symptomatology in adult vitelliform macular degeneration consisted of decreased vision and metamorphopsia. The visual acuity was found to be symmetrical in most cases. In 3 cases (1, 6, 7) a more hyperopic correction could improve the vision, which suggested a slight elevation of these macular lesions. In later stages of the disease there was little change in visual acuity in spite of the changing ophthalmoscopic and angiographic appearance. Acuity was generally better than 20/80, but may slowly decline with severe degenerative changes. Colour vision was found to be normal in most instances, though late stages of the disease showed a red-green anomaly.

One cannot predict the evolutionary genetic patterns from our series of patients in spite of the examination of family members. However, there appeared to be a familial predisposition in 1 family (cases 7 and 8). We suggest that all family members of patients with vitelliform-like lesions are examined ophthalmoscopically.

Fluorescein angiographic patterns may vary. The most common angiographic finding in the initial presentation of this entity is perifoveal hyperfluorescence from pigment epithelial window defects, which is caused by focal pigment epithelial atrophy and dispersion. Pigment epithelial dispersion is commonly associated with clumping of RPE. The foveolar region remains physiologically hypofluorescent. Fishman *et al.*, in their cases of pseudovitelliform degeneration, indicated that peri-

foveolar capillary leakage accounted for hyperfluorescence.¹³ Further follow-up and fluorescein angiogram of case 2 by stereo angiography revealed the leakage was subretinal rather than from the perifoveal capillary network. If retinal leakage of dye did indeed occur, one may expect a cystoid type configuration.

As the adult vitelliform lesion matures, an increase in subretinal exudation is noted. This accounts for the late subretinal leakage of dye presumably from the choriocapillaris. Subretinal haemorrhage or angiographic evidence of subretinal neovascularisation was not found in our cases. The natural history of the mature adult vitelliform lesion further varies. In 1 case (2) loss of RPE and choriocapillaris led to a clinical and angiographic picture of central areolar choroidal sclerosis. However, in 5 cases (3, 6, 8, 9, and 10) the adult vitelliform lesion disappeared and more closely resembled dry atrophic macular degeneration. Three cases (5, 9, 10) had coexistent paracentral drusen.

These clinical and angiographic changes did not correlate significantly with changes in visual status. Fluorescein angiography should be utilised to differentiate other causes of vitelliform-like lesions as well as to ascertain the natural course.

Gass described in his series a central hyperpigmented spot in the fovea, presumed to be secondary to retinal pigment epithelial clumping.¹¹ A similar finding was found in our cases (1, 2, 3, 4, 7). Three of these patients did not show this finding in the initial examination. However, the central foveal hyperpigmentation did occur in the natural course of the disease on an average of 2 to 3 years later.

Electrical studies are useful in separating Best's disease from adult vitelliform macular degeneration. Krill found cases of retinal pigment epithelium and sensory retinal detachment having normal to slightly subnormal EOGs.¹⁵ In senile macular degeneration and dominant drusen he found normal EOGs. The findings in our patients were consistent with those found in dry atrophic macular degeneration. An extinguished or markedly subnormal EOG, which is found in Best's disease, was not found in our cases. For those patients in whom a familial tendency is a consideration electrical studies further delineate true vitelliform dystrophy from adult vitelliform macular degeneration (see Table 1).

Without histopathological studies the location and the natural course of events cannot be proved. The initial degenerative process may be in the retinal pigment epithelium or choriocapillaris. Gass found histological evidence of depigmentation, degeneration, and disruption of retinal pigment epithelium centrally.¹¹ Also, periodic-acid-Schiff-

Table 1 *Differentiation of adult vitelliform macular degeneration from vitelliform macular dystrophy*

	<i>Vitelliform dystrophy</i>	<i>Adult vitelliform degeneration</i>
Age on onset	Prior to 2nd decade	Greater than 40 years of age
Size of lesion	$\frac{1}{2}$ –3 disc diameters	$\frac{1}{3}$ – $\frac{1}{2}$ disc diameters
Symmetry	++	+++
Visual acuity	Initially normal or slightly subnormal	Initially 20/30–20/80
	Variable decline eventual	Slow progression, vision visually stable
Colour vision	Red-green anomaly in late stages	Red-green anomaly in late stages
Fluorescein angiography	Vitelliform lesion hypofluorescent	Vitelliform lesion with ring-like RPE window defect
EOG	Subnormal	Normal
Genetic aspects	Autosomal dominant	No definitive pattern

positive subpigment epithelial deposition of eosinophilic material was seen paracentrally. We believe that the primary pathological process in adult vitelliform macular degeneration is at the level of the retinal pigment epithelium as shown by fluorescein angiography. However, as the disease progresses, there may be additional degeneration of the choriocapillaris.

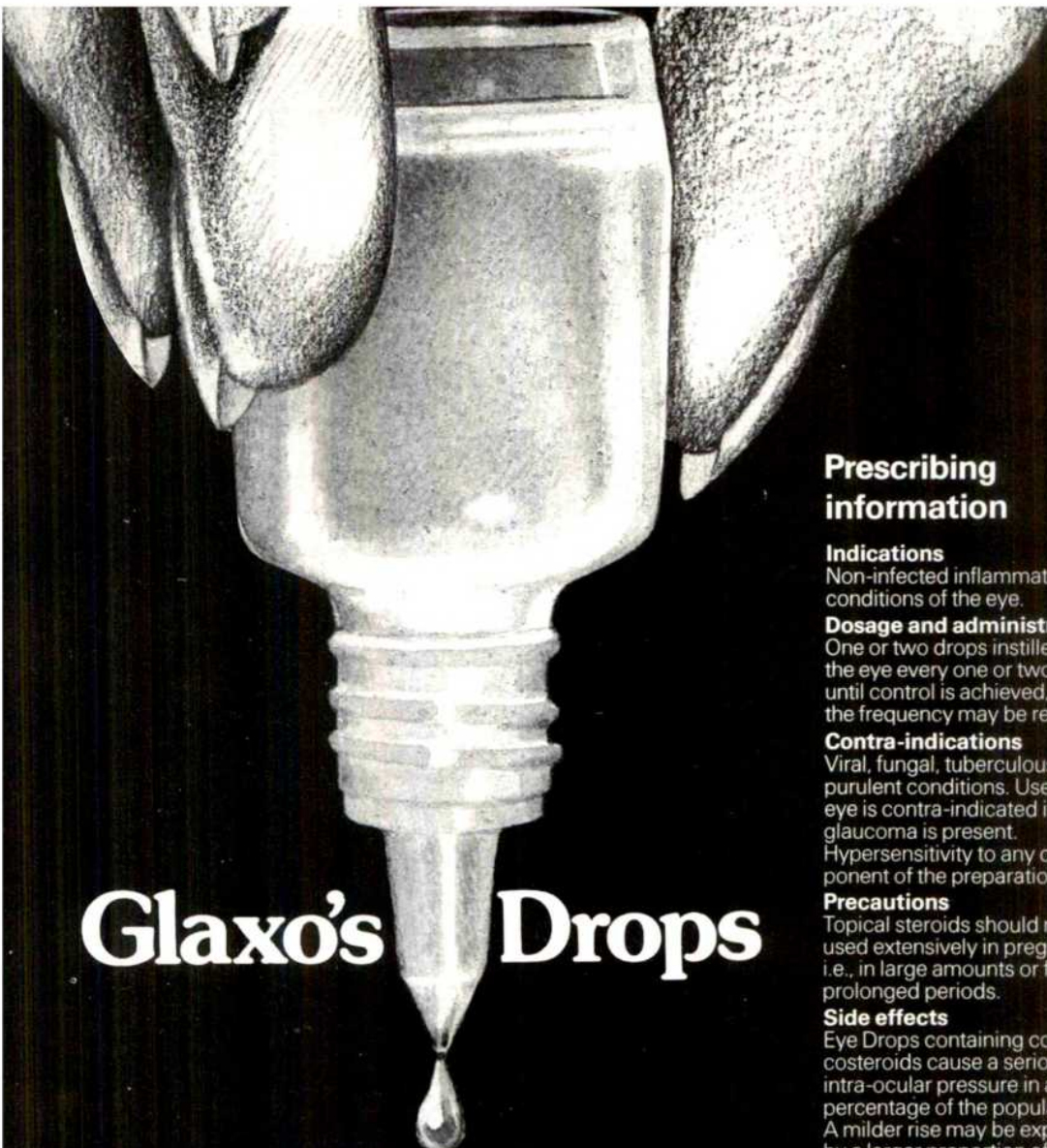
The natural progression of the disease shows that there is a change in the clinical as well as angiographic findings in most patients, especially in the later years of life. The visual acuity, however, usually did not markedly decrease. The eventual clinical picture in 5 cases was indistinguishable from that of dry atrophic macular degeneration. Three patients had coexistent paracentral typical drusen. It is our belief that adult vitelliform macular degeneration is a form of dry atrophic macular degeneration. The adult vitelliform lesion may be equal to macular drusen in forecasting the eventual

clinical picture and natural history of dry atrophic macular degeneration. However, none of our patients showed exudative macular degenerative changes in spite of being followed up for periods of more than 5 years.

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Permanent retinal damage following massive dapsone overdose

D. J. KENNER, K. HOLT, R. AGNELLO, AND G. H. CHESTER

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SUMMARY A massive dose of 7.5 g of 4,4'-diamino, diphenyl sulphone (dapsone) taken as a suicide attempt in a patient on long-term therapy for tuberculoid leprosy resulted in permanent bilateral retinal necrosis, a previously unreported side effect of this drug. The patient developed a severe haemolytic anaemia, methaemoglobinaemia, and acute renal failure requiring peritoneal dialysis. It is proposed that the retinal damage was due to a combination of severe hypoxaemia and the physical effects of red cell fragmentation producing vascular occlusion in the macular and perimacular region, with consequent ischaemic necrosis.

4,4'-Diamino, diphenyl sulphone (4,4' DDS) has been used in the treatment of leprosy since 1941. Reported side effects are predominantly haematological, and include methaemoglobinaemia, agranulocytosis, and haemolytic anaemia.¹⁻⁵ However, overdoses of dapsone have rarely been described.⁶⁻⁸ The present case report describes a massive overdose of 4,4' DDS taken as a suicide attempt. Side effects included previously unreported permanent macular damage.

Case report

A 31-year-old Burmese man was admitted to Royal Perth Hospital in October 1978 having ingested a total of 7.5 g of 4,4' DDS in a suicide attempt. The drug was commenced in 1975 for tuberculoid leprosy, histologically confirmed on skin biopsy, and the patient had been maintained on 50 mg daily before admission. Physical examination on admission revealed an ill-looking man with obvious bluish-grey cyanosis of the tongue, lips, and extremities. The pulse was 108/min and the blood pressure 130/85 mmHg. The remainder of the general examination, including ophthalmoscopy, revealed no abnormality. Blood obtained at venesection was a dark chocolate brown colour and on analysis yielded a total haemoglobin content of 145 g/l and a methaemoglobin of 46 g/l. The blood urea was 7.1 mmol/l (normal 3-8) and the creatinine 111 μ mol/l (normal 50-120). The urine was a deep wine red colour,

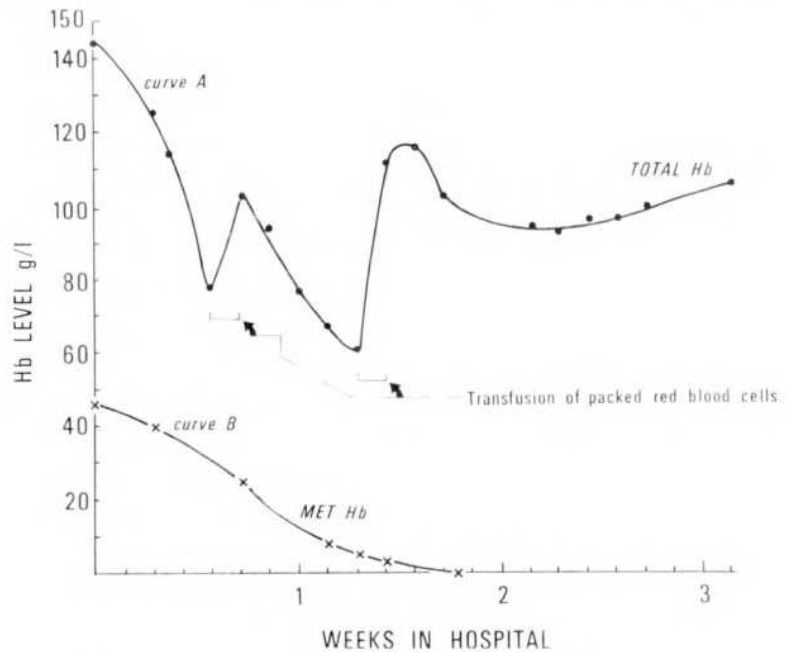
and free haemoglobin was present, with no red cells seen on microscopical analysis.

Four days after admission to hospital the haemoglobin level had fallen precipitously to 78 g/l and the white blood cell count had risen to 38.5×10^9 /l. A peripheral blood film was consistent with a severe haemolytic process, showing crenated, distorted, and fragmented cells, polychromasia, Howell-Jolly bodies, and grossly dysplastic erythroblasts. A coagulation profile was normal. Although initial screening tests for the presence of glucose-6-phosphate dehydrogenase deficiency were negative, subsequent follow-up studies disclosed the milder form (type A) of the condition.

The subsequent clinical course of the patient was one of massive intravascular haemolysis, requiring transfusion with 6 units of packed red blood cells, and severe methaemoglobinaemia (Fig. 1), which was treated with methylene blue and ascorbic acid intravenously. Acute renal failure supervened eventually, requiring peritoneal dialysis (Fig. 2). The patient remained critically ill for over a week and required vigorous supportive therapy. Two weeks after admission he complained of blurred vision. Visual acuity was 6/36 in each eye with no significant refractive error. The ocular abnormalities were confined to the posterior pole of the retina of each eye, and consisted of a bilateral yellow-white appearance of the retina in the macular and paramacular region, with several minute intraretinal haemorrhages in the adjacent normal retina. There was no macular oedema or serous retinal detachment. Fluorescein angiography showed nonperfusion in the region of the yellow-white retina, with

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Fig. 1 Changes in the total haemoglobin level (curve A) and methaemoglobin level (curve B) during hospital admission.



abrupt termination of the venules and arterioles surrounding the site (Fig. 3). Normal perfusion was present in the retinal periphery, which was also ophthalmoscopically normal.

It was thought that the ophthalmoscopic appearance of the macula and the fluorescein angiogram

changes indicated that necrosis of the macular region had taken place. The patient was started on systemic prednisolone therapy, 75 mg per day for 1 week, and then on a reducing dosage for 1 month. During the course of the next 3 weeks the yellow-white appearance of the macula faded and was

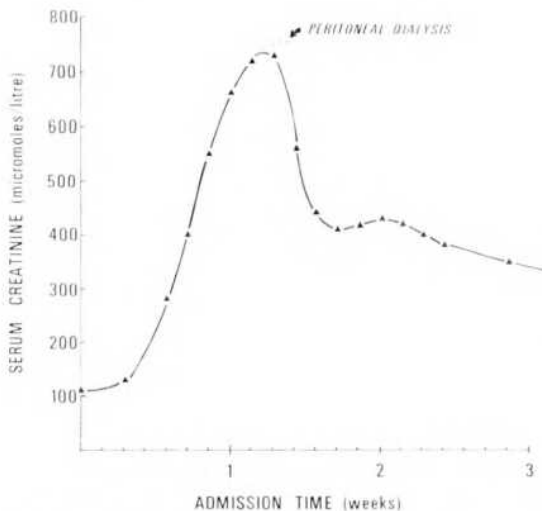


Fig. 2 Changes in serum creatinine level during hospital admission. Arrowed bracket indicates peritoneal dialysis. Shaded area represents the normal range of serum creatinine.

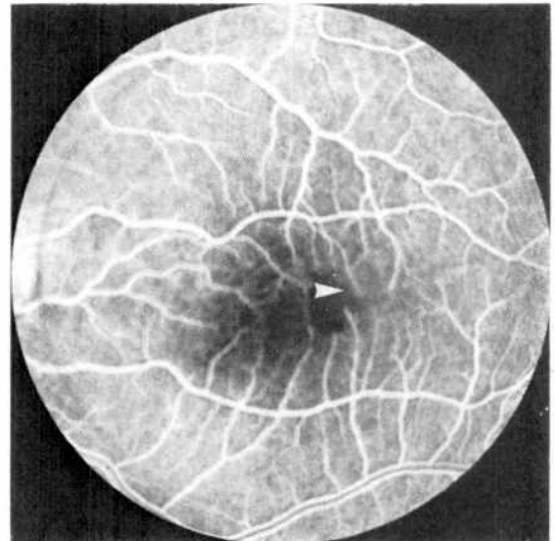


Fig. 3 Fluorescein angiogram of left eye 2 weeks after the acute episode showing capillary closure in the paramacular region with abrupt termination of the arterioles and venules (arrowed).

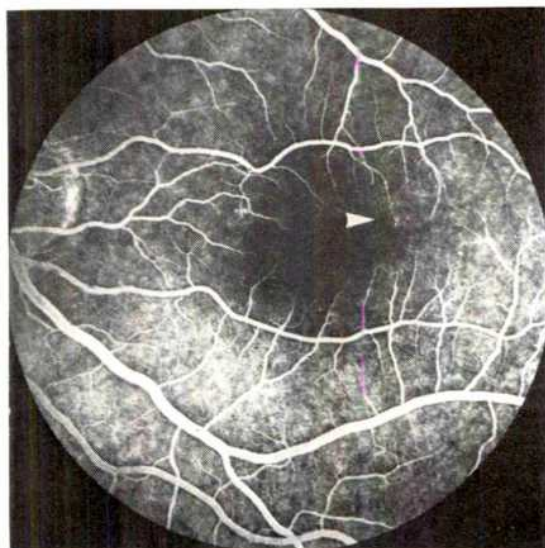


Fig. 4 Fluorescein angiogram of left eye 7 months after the acute episode. Revascularisation of the paramacular region has occurred, with the development of an abnormal looped vessel on the edge of the previously avascular zone (arrowed).

replaced by the more normal orange colouration. The normal macular light reflex and luteal pigment did not reappear, and there was a minimal pigmentary change in the retinal pigment epithelium. Three weeks after the blurred vision had been noted the visual acuity had improved to 6/18 in each eye, and no further improvement has occurred. Fluorescein angiography 7 months after the event showed revascularisation of the macula and the perimacular region. In the left eye, on the edge of what was the avascular zone, an abnormal looped blood vessel had appeared (Fig. 4).

Discussion

The absence of retinal damage in other cases of dapsone poisoning⁶⁻⁸ and the restriction of the retinal necrosis to the macular region in this patient, makes a direct toxic effect of the dapsone unlikely. It is more probable that the macular damage was ischaemic in origin from a combination of acute severe peripheral hypoxaemia and the physical effects of red cell fragmentation, consequent upon the haemolytic process, interfering with the macular blood supply.

The haematological side effects of dapsone include methaemoglobinaemia, agranulocytosis, and haemolytic anaemia,¹⁻⁵ which is usually mild but may be more severe in the presence of glucose-6-phosphate dehydrogenase deficiency.³ Haemolysis

is probably due to intracellular oxidant activity of the drug.⁴ Probably in this patient the equivalent of the total red cell circulating mass was haemolysed, and the rate of haemolysis appeared unaffected by transfusion (Fig. 1). It can be inferred that almost all the red cells were damaged and therefore potentially defective in terms of oxygen carrying capacity. In addition, on admission to hospital a methaemoglobin level of 46 g/l, representing some 40% of the total haemoglobin, was present (curve B, Fig. 1), which would have had the effect of even further lowering the potential blood oxygen-carrying capacity. Thus it seems likely that profound tissue hypoxia was present in this patient, probably when he was admitted to hospital. We believe that this profound hypoxia was a major aetiological factor in the macular changes observed.

The physical effects of red cell fragmentation causing macular vascular occlusion may also have been a significant factor. The macula nonperfusion seen on the fluorescein angiogram is similar to the macular vascular changes reported in sickle cell disease.⁹⁻¹² This effect has been attributed to a sludging effect of the sickled red cells,¹³⁻¹⁷ and the macular capillaries may be especially susceptible owing to their small calibre and considerable length.¹⁸ Fragmented red cells are regularly seen in patients on dapsone, particularly at dosage levels of 100 mg and above,¹⁹ but the cause is unclear; it does not appear to be related to microangiopathy or mechanical trauma. Although central vision can be preserved in the presence of macular capillary closure,^{10 11 20 21} the red cell fragmentation consequent upon the massive haemolysis combined with the severe hypoxaemia may have been sufficient to produce macular changes. The abnormal looped vessel on the edge of the previously avascular area (Fig. 4) is of interest. It probably represents abnormal blood vessel regeneration and is similar to some of the perimacular vascular changes seen in sickle cell disease.¹¹

If a massive overdose of dapsone with intravascular haemolysis and a sickle cell crisis are comparable events, it is possible that dapsone at normal dosage levels may produce foveal capillary changes similar to the usually asymptomatic foveal vascular disruption seen in 29% of patients with sickle cell disease.¹¹ We conclude that all patients experiencing blurred vision while on dapsone therapy should therefore be subjected to careful assessment of their macular function, including fluorescein angiography. Our experience would also suggest that physicians would be wise to screen patients for the presence of glucose-6-phosphate dehydrogenase deficiency before embarking upon therapy with dapsone.

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Oxygen dissociation curve in Eales's disease

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SUMMARY The oxyhaemoglobin dissociation curve (ODC) was investigated in 15 patients with Eales's disease and 11 controls to test the hypothesis that Eales's disease is caused by retinal hypoxia secondary to impaired oxygen release from the blood. Patients with the peripheral form of Eales's disease did not have any significant difference in their P_{50} values when compared with the controls. However, the P_{50} values were significantly lower ($P < 0.005$) for the patients with mixed retinopathy. This degree of increased oxygen affinity is not physiologically significant but may reflect an intrinsic abnormality of the red cells in these cases.

Retinal perivasculitis is a descriptive term applied to conditions where there is sheathing and occlusion of the retinal vessels which may be associated with retinal haemorrhages, new vessel growth, and vitreous haemorrhages which ultimately lead to retinal detachment, cataract, and glaucoma. Many of these cases are secondary to uveitis or systemic disease, but in the majority retinal perivasculitis occurs as a primary or idiopathic condition of the eye. These patients may be considered to have Eales's disease, since they typify his original description^{1,2} of 'primary retinal haemorrhages in young men'. This appears to be a noninflammatory condition and is the subject of this paper. However, it must be stressed that Eales's disease is a descriptive term which probably shelters many entities.

Eales's disease usually affects healthy males between the ages of 20 and 30 years, but it may occur at any age and also in females. The clinical appearances may range from those of peripheral vessel closure and new vessel growth resembling sickle cell retinopathy (Fig. 1) to those of diffuse vascular disease and disc neovascularisation similar to diabetic retinopathy (Fig. 2). The disease is often characterised by tortuosity, beading, and sheathing of the vessels. Both eyes are usually affected, but the condition may be unilateral.

Despite prolonged interest³ the aetiology of Eales's disease remains obscure. However, the clinical picture suggests a hypoxic process affecting the retina. Factors involved in tissue oxygenation include pulmonary function, cardiac output, and

the oxygen affinity of the blood. Patients with Eales's disease apparently have normal cardiac and pulmonary function, so we decided to investigate the oxygen affinity of their blood.

Hypothesis

Impaired oxygen release from the erythrocytes may be a factor in the aetiology of Eales's disease.

In man, oxygen is transported bound to haemoglobin within the erythrocytes. Haemoglobin exists in 2 forms, oxyhaemoglobin and deoxyhaemoglobin, and the relationship of the 2 is best described by the oxyhaemoglobin dissociation curve (ODC, Fig. 3), in which the percentage oxygen saturation of haemoglobin is plotted against the partial pressure of oxygen. The ODC has a sigmoid shape because the affinity of haemoglobin for oxygen increases as the molecules of oxygen sequentially combine. This provides a very efficient oxygen transport system because at alveolar oxygen tension (P_{O_2} , 90-100 mmHg) the curve is flat and the oxygen tension has to fall by 25-30 mmHg before there is significant oxygen release. The ODC has a steep slope at tissue P_{O_2} (approximately 40 mmHg) and a small change in oxygen tension would have a large effect on oxygen release. Oxygen affinity is usually indicated by the P_{50} value which is that P_{O_2} at which the haemoglobin is half saturated. Under standard conditions of 37°C temperature and pH 7.4 the P_{50} value for normal whole blood is 26.6 mmHg.

An increase in oxygen affinity (low P_{50}) means that less oxygen is released for a given fall in P_{O_2} and will shift the ODC to the left. Conversely a decrease in oxygen affinity (high P_{50}) means that

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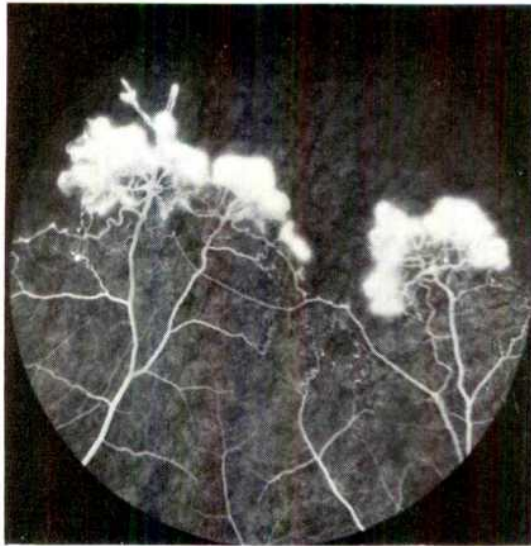


Fig. 1 Case 4, peripheral vessel closure and new vessel growth resembling sickle cell retinopathy.

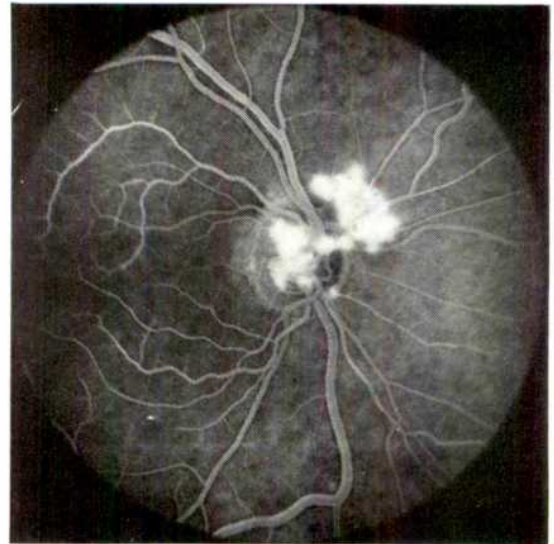


Fig. 2 Case 12, disc neovascularisation similar to diabetic retinopathy.

more oxygen is released for a given fall in P_{O_2} and there is a right shift of the ODC.

The oxygen affinity of the blood not only reflects the intrinsic nature of the haemoglobin but is also subject to modification by certain intracellular ligands. These include hydrogen ions, carbon dioxide, and organic phosphates, especially 2,3-diphosphoglycerate (2,3-DPG). Hydrogen ions and carbon dioxide decrease oxygen affinity (high P_{50}) with a right shift in the ODC. Alkalosis increases oxygen affinity (low P_{50}) and the ODC shifts to the left. The shift in the position of the ODC caused by pH change is known as the Bohr effect. 2,3-DPG is an organic phosphate produced by red cell glycolysis. It reduces oxygen affinity by combining preferentially with deoxyhaemoglobin and through the Bohr effect by lowering the intraerythrocyte pH. The rate of erythrocyte glycolysis is geared to produce a level of 2,3-DPG that will oppose any shift in the ODC. For example, the level of 2,3-DPG is low in acidotic states.

Factors involved in oxygen transport include pulmonary function, cardiac output, haemoglobin concentration, and oxygen affinity. These are in equilibrium in order to maintain normal tissue oxygenation, and when one is altered the others compensate. For example, in anaemia there is an increase in breathing and cardiac output. There is also an increase in the level of 2,3-DPG in the erythrocytes, which shifts the ODC to the right (high P_{50}) and so decreases the oxygen affinity. Erythrocytes with abnormal oxygen affinity com-

pensate by changes in their haemoglobin concentration. Low oxygen affinity (ODC shifted to the right, high P_{50}) causes the haemoglobin concentration to be lower, whereas high oxygen affinity (ODC shifted to the left, low P_{50}) causes an increased haemoglobin concentration. This compensatory response is mediated through the haemopoietic system.

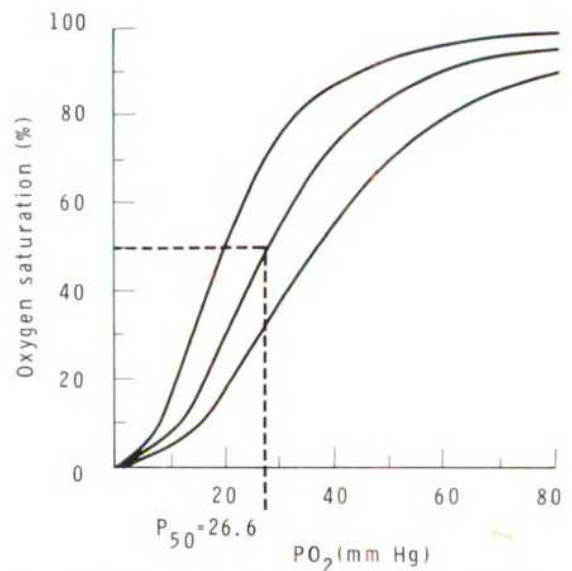


Fig. 3 The oxyhaemoglobin dissociation curve (ODC) illustrating the effects of left and right shifts.

Table 1 Patients with Eales's disease

Case	Age	Sex	Type of Eales	Hb (g/dl)	PCV	Retics	P ₅₀ (mmHg)	n	DPG (μmol/g)	Hb electrophoresis
1	25	M	Mixed	15.5	47	1.6	29.0	2.8	11.68	AA
2	57	F	Mixed	15.6	45	2.6	29.0	2.8	11.16	AA
3	44	M	Mixed	16.6	48	1.0	28.0	2.9	12.00	AA
4	38	F	Peripheral	15.4	45	1.2	28.0	2.8	16.74	AA + Hb F 3%
5	23	M	Mixed	14.9	44	0.4	28.0	2.3	10.42	AA
6	55	M	Mixed	15.00	45.5	0.4	28.5	2.7	15.04	AA
7	38	M	Mixed	17.2	49.6	0.6	28.5	2.7	13.76	AA
8	36	F	Peripheral	11.2	33.5	0.8	28.0	2.8	15.33	Hb AD
9	48	M	Peripheral	16.0	45.5	1.0	30.0	2.5	13.22	AA
10	38	M	Peripheral	14.2	41.1	1.0	31.0	3.0	13.95	AA + 5% Hb F
11	34	F	Mixed	13.4	40.3	0.2	29.5	2.7	17.07	AA
12	51	M	Mixed	16.6	50.0	0.4	27.5	2.7	12.47	AA
13	50	M	Peripheral	15.7	43.0	1.2	31.0	2.7	15.38	AA
14	64	M	Peripheral	14.4	43.0	0	27.5	2.6	10.9	AA
15	46	M	Peripheral	13.8	42.0	0	30.25	2.9	14.34	AA

P₅₀, washed red cells at pH 7.00; normal 29.5–32.00 mmHg. n, Hill's constant; normal 2.6–2.9.

Although these compensatory responses are adequate in general, the retina may become hypoxic (in cases with impaired oxygen release) owing to the special nature of its circulation and metabolism. The retina is particularly vulnerable to hypoxia due to the small calibre and endarterial nature of its blood supply, which has to function at pressures above the intraocular tension. Moreover the retina has a very high metabolic rate, which requires a rich oxygen supply. Retinal hypoxia would be worse on the venous side of the capillary bed and would cause dilatation of the vessels with slowing of blood flow. This combined with a raised haematocrit would increase the viscosity in these vessels and may lead to their occlusion. Hypoxia may also damage the vessel walls directly and cause thickening and proliferation of the endothelium with ultimate occlusion. This pathogenesis has been suggested for diabetic retinopathy by Ditzel.⁴ New vessels would grow in response to retinal hypoxia and may cause recurrent vitreous haemorrhages, so fulfilling the criteria for Eales's disease.

Patients and methods

Fifteen patients with Eales's disease were studied. These were all cases of retinal neovascularisation of unknown aetiology without associated systemic disease or uveitis. In particular, diabetes, hyperten-

sion, sickle cell disease, sarcoidosis, tuberculosis, and syphilis were excluded by clinical examination, glucose tolerance tests, haemoglobin electrophoresis, Mantoux, Kveim, and VDRL tests and chest x-rays. All these patients were examined and were broadly categorised as peripheral or mixed types of Eales's disease (Table 1) according to the pattern of retinal vessel closure and neovascularisation seen on fluorescein angiography. An additional case was kindly provided by Professor Patz, of the Wilmer Institute.

The control group consisted of 11 members of the hospital staff who had no ocular symptoms (Table 2), but their fundi were not examined.

A sample of venous blood was taken from each of the patients and controls. Routine haematological parameters were measured including haemoglobin concentration, full blood count, and haemoglobin electrophoresis.

The ODC was determined in all our cases by a spectrophotometric method using washed red cells in a phosphate buffer at pH 7.00.⁵ The curve was determined for each patient and a control at the same time, though in some cases 1 control acted for 2 patients. The P₅₀ value and Hill's constant⁶ were derived from each curve. The intraerythrocyte level of 2,3-DPG was measured for each sample at the same time as the ODC was determined.

In 2 of our cases (cases 3 and 12) the ODC was

Table 2 Controls

Control	Age	Sex	Hb (g/dl)	PCV	Retic	P ₅₀ (mmHg)	n	DPG (μmol/g)	Hb electrophoresis
1	37	F	14.2	40.8	0.6	29.5	2.7	14.29	AA
2	39	M	17.6	52.1	0.4	28.75	2.6	13.2	AA
3	35	M	15.1	45.3	0.6	29.5	2.8	13.83	AA
4	32	M	14.00	40.0	0	31.0	2.9	14.94	AA
5	30	M	14.5	44.0	0	27.5	2.8	12.22	AA
6	49	F	12.0	36.0	0	30.0		16.33	AA
7	33	M	14.9	45.0	0	29.5	2.8	12.87	AA
8	33	F	14.1	42.5	0.4	30.0	2.7	14.70	AA
9	37	M	16.1	47	2.4	30.75	2.8	12.94	AA
10	38	M	14.7	44	0	30.5	3.0	11.54	AA
11	32	M	15.5	46	0	31.0	2.8	13.37	AA

P₅₀, washed red cells at pH 7.00; normal 29.5–32.0 mmHg. n, Hill's constant, normal 2.6–2.9.

also determined for whole blood by a microtechnique (P. D. Wimberley, personal communication). In the additional case provided by Professor Patz the ODC was determined for whole blood by the Hem-O-Scan auto analyser (Aminco).

Results

Tables 1 and 2 summarise the clinical and haematological findings in our 15 patients and 11 controls respectively. Comparison of the 2 groups (Table 3) showed that the P₅₀ values were significantly lower in patients with mixed but not in those with the peripheral types of Eales's disease. The haemoglobin and 2,3-DPG levels were not significantly different.

The P₅₀ values for whole blood were also low in 2 of our patients (cases 3 and 12, Table 4) and also in Professor Patz's patient (Table 5).

Discussion

Patients with Eales's disease may be considered to have neovascular retinopathies of unknown aetiology. Although the fundamental cause of the retinal neovascularisation is not known, there is considerable evidence for a hypoxic process.^{7,8} If this process is operative in Eales's disease, we must explain the cause of the underlying retinal hypoxia.

Patients with Eales's disease are usually fit young men whose disease is apparently confined to their retinal vessels. Other vascular systems do not appear to be affected, which suggests that it is not a disease of the blood vessels themselves.

Alternatively, Eales's disease could be due to

Table 3 Comparison of the patients and controls in Tables 1 and 2

	Number of cases	Hb g/dl	P ₅₀ mmHg	DPG μmol/g
Cases:				
Mixed	8	15.6±1.2	28.5±0.7	12.95±2.22
Peripheral	7	14.4±1.6	29.4±1.5	14.27±1.87
Both	15	15.0±1.5	28.9±1.2	13.56±2.1
Controls	11	14.8±1.4	29.8±1.0	13.66±1.35
Compare*:				
Mixed vs. controls		NS	P<0.005	NS
Peripheral vs. controls		NS	NS	NS
Both vs. controls		NS	<0.05	NS

*Wilcoxon rank sum test. NS, not significant.

Table 4 Details of whole blood oxygen affinity in 2 of our patients

Case	P ₅₀ (mmHg)	n	Bohr shift
3	23.8	2.0	
12	25.0	2.0	-0.55

P₅₀ at Ph 7.4; normal 25.5–27.75 mmHg. n, Hill's constant; normal 2.6–2.9.

Table 5 Professor Patz's patient

Age	Sex	Type of Eales	Hb (g/dl)	PCV	P ₅₀ (mmHg)
53	M	Mixed	17.6	55	22.7

P₅₀, whole blood at pH 7.4; normal 26.5.

changes in the blood which affect the retina only owing to the special nature of its circulation and high metabolic requirements. Eales's disease is usually bilateral, which also implies a systemic condition.

The similarity between some cases of Eales's disease and sickle cell retinopathy suggests a haematological aetiology. Haemoglobin electrophoresis is usually normal, although occasionally abnormal haemoglobins are found (case 8, Hb D, and cases 4 and 10, HbF).

Acanthocytosis in patients with Eales's disease has been reported.⁹⁻¹¹ This is an abnormality of the erythrocytes where there are thorny protuberances on the surface membrane. Acanthocytes may be more rigid than normal erythrocytes and obstruct the small retinal blood vessels, as occurs in sickle cell disease. Acanthocytosis was not noted in our patients.

Argarwal *et al.*¹² found that in 61 out of 70 cases of Eales's disease the oxygen content per gram of haemoglobin was reduced. Their patients had normal electrophoresis, but unfortunately they did not report the haemoglobin concentrations.

An observation that the haemoglobin concentration tended to be higher in patients with Eales's disease than in a control group with uveitis (E. S. Perkins, personal communication) suggested that this relative polycythaemia could be secondary to impaired oxygen release from the red cells. We therefore investigated the ODC in our patients.

In our cases the ODC was determined by a spectrophotometric method using washed red cells in isotonic phosphate buffer at pH 7.00. This method showed that the mean P_{50} values were 29.4 ± 1.5 mmHg in the patients with the peripheral type of Eales's disease, 28.5 ± 0.7 mmHg in the patients with mixed retinopathy, and 29.8 ± 1.0 mmHg in the control groups. Compared with the controls the P_{50} value was significantly lower in the patients with the mixed type of Eales's disease ($P < 0.005$) but not in the patients with the peripheral form of Eales's disease.

This method for determining the ODC is particularly suited for detecting haemoglobin abnormalities, but metabolic causes for shifts in the ODC may be missed. Therefore in each case the intra-erythrocyte level of 2,3-DPG was measured at the same time as the ODC was recorded. The mean level of 2,3-DPG was 13.56 ± 2.1 $\mu\text{mol/g}$ in the patients with Eales's disease and 13.66 ± 1.35 in the control groups. There was no significant difference between the 2,3-DPG levels in the 2 groups, which suggests that there was no metabolic cause for a shift in the ODC.

Nor was there any significant difference between

the haemoglobin levels of the patients and the controls. This was not in keeping with Professor Perkins's earlier observation that there was a relative polycythaemia in patients with Eales's disease.

The ODC for whole blood is a more physiological expression of oxygen affinity and would be likely to show changes due to abnormal metabolism. Two of our patients (cases 3 and 12) had their whole blood curves determined by a micromethod (Wimberley, personal communication), and Professor Patz's patient had his ODC determined for whole blood by the Hem-O-Scan analyser (Aminco). All 3 cases had mixed retinopathy and low P_{50} values for whole blood at pH 7.4 (Tables 4 and 5).

Although our patients all have the diagnosis of Eales's disease, it is likely that they represent several different conditions. Those with the peripheral type of clinical picture resemble sickle cell disease, and this suggests an obstructive aetiology. These patients did not have significantly different P_{50} values when compared with the control group, whereas the patients with the mixed type of Eales's disease resembling diabetic retinopathy had significantly lower P_{50} values ($P < 0.005$). However, this degree of increased oxygen affinity is not physiologically significant but may reflect an intrinsic abnormality of the red cells. Erythrocyte metabolism has 2 main functions: firstly, to carry and deliver oxygen to the tissues, and secondly to maintain the biconcave shape of the cell which gives it the necessary flexibility to negotiate the fine capillary channels. The low P_{50} values in some of our patients may simply be an expression of altered erythrocyte metabolism. It would be interesting to know if erythrocyte rigidity or membrane proteins are abnormal in Eales's disease.

We are grateful to the surgeons at Moorfields Eye Hospital for permission to investigate their patients. We thank Dr A. Winder for his advice and encouragement and Dr P. D. Wimberley, who measured the whole blood oxygen dissociation curves in 2 of our patients. Thanks are also due to Dr J. D. Buckley for statistical analysis, Mr K. Sehmi for the illustrations, Dr M. F. Goldberg for advice, and Miss C. Willoughby for typing the manuscript.

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Leber's optic neuropathy: clinical and visual evoked response studies in asymptomatic and symptomatic members of a 4-generation family

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SUMMARY A clinical and neuro-ophthalmological examination using tests of visual acuity, quantitative visual field analysis, tests of colour discrimination, ophthalmoscopy, and pattern visual evoked responses was performed on 2 symptomatic and 16 asymptomatic members of a family with Leber's optic neuropathy. The visual evoked responses were abnormal in the 2 clinically affected males and in 1 asymptomatic male. Tests of colour discrimination with Ishihara plates, the Farnsworth-Munsell 100 hue test, and the Nagel anomaloscope revealed abnormalities in 8 asymptomatic family members, with the Farnsworth-Munsell test proving to be the most sensitive to mild abnormalities of colour discrimination. The occurrence of detectable neuro-ophthalmological abnormalities within this family is in keeping with the expected pattern of transmission of Leber's optic neuropathy. The significance of detection of presymptomatically affected cases and asymptomatic carriers is discussed.

A familial type of optic neuropathy first described by Theodore Leber in 1871¹ affects predominantly young males and causes an acute or subacute failure of vision affecting both eyes, though not usually simultaneously, leading eventually to optic atrophy.

Leber's optic neuropathy is inherited in a unique fashion. The pattern of inheritance, first thought to be an X-linked disorder, does not conform to Mendelian principles.²⁻⁴ Various hypotheses put forward as alternatives to Mendelian inheritance include the vertical transmission of some infectious agent such as a slow virus^{5,6} or similar agent through the female parent via the maternal ooplasm^{7,8} or transplacentally.⁹

The finding of neuro-ophthalmic and visual evoked response abnormalities in some asymptomatic members of a family with Leber's optic neuropathy¹⁰ suggests that the detection of asymptomatic carriers and presymptomatically affected cases is possible.

The present study seeks to define the nature and incidence of neuro-ophthalmological abnormalities

in both symptomatic and asymptomatic members of a family with Leber's atrophy by recording the visual evoked responses and carrying out a clinical neuro-ophthalmological examination, with detailed testing of colour vision.

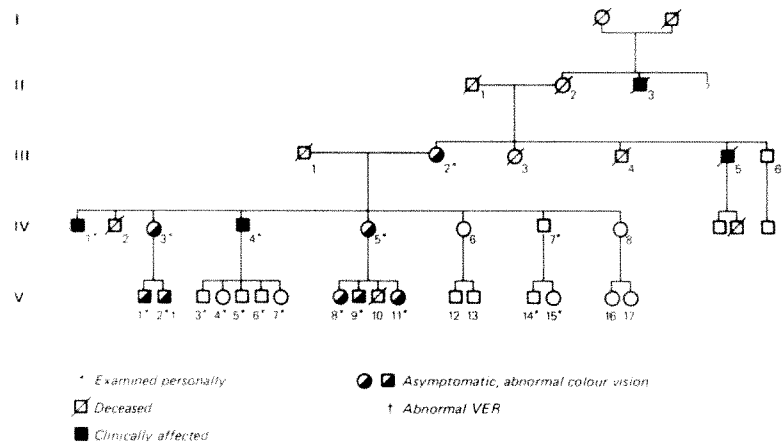
Patients and methods

We studied 2 affected males and 16 asymptomatic members in a 4-generation family with Leber's optic atrophy (Fig. 1). Hospital records on 2 deceased affected cases (II₃, III₆) are consistent with the diagnosis of Leber's optic atrophy in that both patients presented at the age of 21 years with a rapid sequential irreversible visual loss in both eyes leading to optic atrophy. No female in this family was known to have had visual loss, and none of the apparently healthy members had any visual symptoms which were not corrected by simple refraction. Of the 2 affected brothers studied (cases IV₁, IV₄) the elder presented at the age of 20 years with failing vision in the right eye followed 1 month later by similar symptoms involving the left eye. Examination at that time showed bilateral central scotomata and disc swelling, which was noted to lead on to blue-grey atrophy of both discs 6 months later. The

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Fig. 1 Pedigree of a family with Leber's optic neuropathy showing symptomatically affected cases and the occurrence of neuro-ophthalmological abnormalities in some of the asymptomatic cases examined.



younger brother (IV₄) had a similar presentation at the age of 21 years with acute visual failure beginning in the right eye followed 6 weeks later by similar symptoms in the left eye, leading irreversibly to optic atrophy.

EXAMINATION

All patients in this study underwent a neuro-ophthalmological examination which included measurement of visual acuity (Snellen charts), quantitative perimetry by the Friedman field analyser, and detailed testing of colour vision with Ishihara plates, the Farnsworth-Munsell (F-M) 100 hue test, and the Nagel anomaloscope. The appearances of the retinal blood vessels and optic discs were noted in each patient. An abnormality on reading the Ishihara plates was noted if 3 or more mistakes were made on presentation of 25 colour plates to each eye. The F-M 100 hue test for colour discrimination was conducted under standardised lighting by the recommended technique.¹¹ Abnormalities on this test were evaluated according to the criteria of Verreist.¹² A Nagel anomaloscope model 1 was used to test the patient's ability to achieve Rayleigh's match: red (570 nm) + green (546 nm) = yellow (589.3 nm). We determined an anomaly quotient (AQ) by comparing the subject's performance with that of an unrelated control subject, using the formula based on the relative mixing of green and red to achieve the yellow match:

$$\frac{\text{Relative width of green slit (test subject)}}{\text{Relative width of red slit (test subject)}} \div \frac{\text{Relative width of green slit (control subject)}}{\text{Relative width of red slit (control subject)}}$$

A value of 1.0 is accepted as normal with a range of 0.95 to 1.05 (mean $\pm$ 2.5 SD) obtained on testing 12 healthy control subjects.

Visual evoked responses (VER) were recorded by using Ag/Ag Cl₂ electroencephalograph electrodes

placed according to the international 10-20 system. The active electrode was at Oz and the reference electrode was at Cz (vertex), and an earth electrode was placed on the forehead. Pattern visual stimulation was provided by a television pattern generator.¹³ The frequency of reversal of the frame locked pattern was 2 Hz, and the transition time for pattern reversal was 20 ms. At the viewing distance used (1.7 metres) the screen subtended angles of 17° 10' (horizontal) and 13° (vertical) at the eye, and each check had a visual subtense of 50'. Contrast was set to maximum and the luminance was kept constant. Occipital responses were averaged by a Medelec MS6 polygraph triggered by each pattern reversal. The average response to 128 reversals was written out on a Phillips PM8041 X-Y recorder. Responses from each eye were obtained to whole-field stimulation. The subjects were requested to fixate on a 5 mm central spot on the television screen, and those with refractive errors wore corrective lenses.

The latencies of the major positive component (P2 or P100) and of the negative peaks (N1, N2) preceding and following the P2 peak were determined. The latency difference between the 2 negative peaks was used as the index of temporal dispersion, and the amplitude was defined as the difference in potential between the N1 and N2 peaks. In addition the P2 latency difference between the 2 eyes was calculated. All these parameters were compared to normal values obtained from 32 healthy subjects by taking the mean $\pm$ 2.5 standard deviations as the upper and lower limits of normal for each of the parameters.

Results

AFFECTED INDIVIDUALS

The two clinically affected males (cases IV₁ and IV₄) both had markedly reduced visual acuities of

Table 1 Summary of the neuro-ophthalmic and visual evoked response findings in both symptomatic and asymptomatic members of a family with Leber's optic neuropathy

Patient	Age	Visual acuity**		Colour discrimination			VER		Fundl	
		R	L	Ishihara plate†	Anomaloscope***† (anomaly quotient)	F-M 100 hue test† (total error score)	R	L	R	L
III ₂	66	6/9	6/6	Abn	1.180	198* Poor discrimination	N	N		Vessel tortuosity
IV ₁	47	6/60	6/60	—	—	—	Flat	Flat	Atr	Atr
IV ₂	42	6/9	6/9	N	—	143* Poor discrimination	N	N	N	N
IV ₄	38	6/60	6/60	—	—	—	Flat	Flat	Atr	Atr
IV ₅	36	6/5	6/6	N	1.00	81 Red-green axis	N	N	N	N
IV ₇	32	6/6	6/6	N	1.00	54 No axis	N	N	N	N
V ₁	21	6/5	6/5	Abn	1.317	116* Peak at blue-green	N	N	N	N
V ₂	18	6/5	6/5	N	1.180	49 Red-green axis	Abn	Abn	N	N
V ₃	17	6/5	6/5	N	1.00	30 No axis	N	N	N	N
V ₄	13	6/5	6/5	N	1.00	32 No axis	N	N	N	N
V ₆	12	6/6	6/9	N	0.95	24 No axis	N	N	N	N
V ₈	11	6/9	6/6	N	1.00	56 No axis	N	N	N	N
V ₇	8	6/9	6/6	N	Not tested	Not tested	N	N	N	N
V ₉	17	6/6	6/6	N	1.247	222* Poor discrimination	N	N	N	N
V ₁₀	13	6/6	6/6	N	1.057	164* Poor discrimination	N	N	N	N
V ₁₁	12	6/5	6/5	N	1.057	170* Poor discrimination	N	N	Temporal pallor	Temporal pallor
V ₁₄	9	6/5	6/5	Not tested	Not tested	Not tested	N	N	N	N
V ₁₅	6	6/5	6/5	Not tested	Not tested	Not tested	N	N	N	N

*Error score abnormal for respective age group. **Snellen chart. ***Normal range 0.95–1.05. †Values are given for the right eye only. No significant difference was obtained by testing the left eye. N = normal. Abn = abnormal. Atr = optic atrophy.

6/60 in each eye and optic atrophy (Table 1). Quantitative perimetry demonstrated bilateral central scotomata. Colour discrimination and visual acuity were so poor that tests of colour vision could not be performed. No recognisable component was present in the visual evoked responses from either eye in these 2 patients. General neurological examination revealed no abnormal signs.

DEFINITE CARRIER

On the basis of the pedigree only 1 person (III₂) who was examined could be positively identified as being a definite carrier. She had no visual symptoms

and no abnormal signs on general neurological examination. Ophthalmoscopy, however, revealed that though disc appearances were normal there was an increase in the tortuosity of the small retinal vessels in each eye. This patient made a significant number of mistakes on the Ishihara plates with each eye, and her anomaly quotient of 1.18 indicated a moderate deuteranomalous (green deficient) match. Her F-M 100 hue test was consistently abnormal on repeated testing, with an abnormal total error score and maximal error in the red green axis (Fig. 2). Her visual fields were normal, as were the visual evoked responses from each eye.

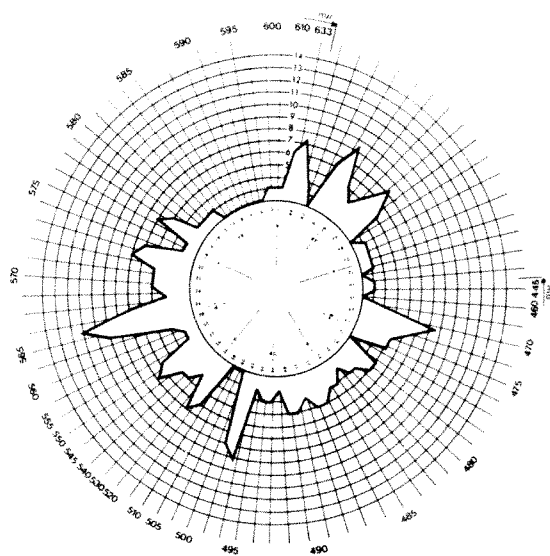


Fig. 2 Case III₂, a definite carrier. Farnsworth-Munsell 100 hue test showing increased total error score and a pattern of generalised poor colour discrimination.

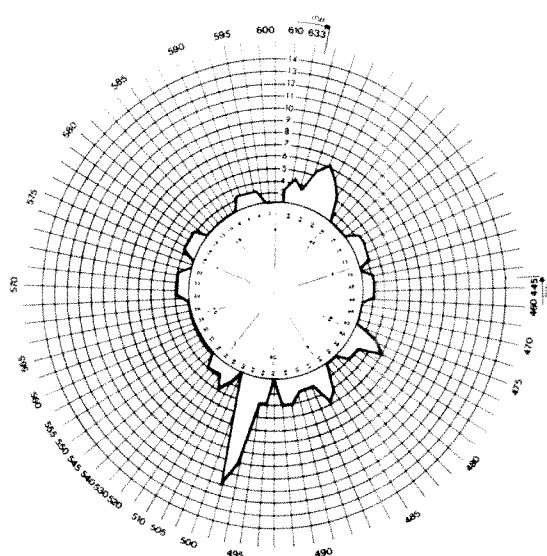


Fig. 3 Case IV₅, a potential carrier. Farnsworth-Munsell 100 hue test with normal total error score but with maximal error in the red-green axis.

POTENTIAL CARRIERS

Two of the daughters of III₂ who are potential carriers were examined. Both were asymptomatic and had normal visual acuity, visual fields, and visual evoked responses. Colour testing, however, revealed abnormalities in both cases. Case IV₃ had an abnormal total error score on the F-M test with a pattern of generalised poor colour discrimination. For logistic reasons she could not be examined with the anomaloscope. Case IV₅ though having a total error score on the FM test within normal limits was shown to have a clear red-green axis on the chart (Fig. 3). Her ability to match red and green on the anomaloscope was normal with an AQ of 1.0. Cases IV₆ and IV₈, who were reported as having no visual symptoms, were not available for study.

OTHER ASYMPTOMATIC INDIVIDUALS

The 5 children (cases V₃-V₇, aged 17-8 years) of one of the affected males (case IV₄) were all examined and found to have normal visual acuities, colour vision, visual fields, and VERs. Case V₇ was too young to co-operate fully with the anomaloscope and F-M tests. Their normal colour tests as exemplified in Fig. 4 were in striking contrast to the abnormalities found in cases V₁ and V₂, who were the sons of IV₃ and at risk of developing the disease. Both these cases had abnormalities on the F-M test with maximum errors in the red green axis (Figs. 5 and 6) and a green-deficient mismatch on the anomaloscope. In addition case V₂ had an

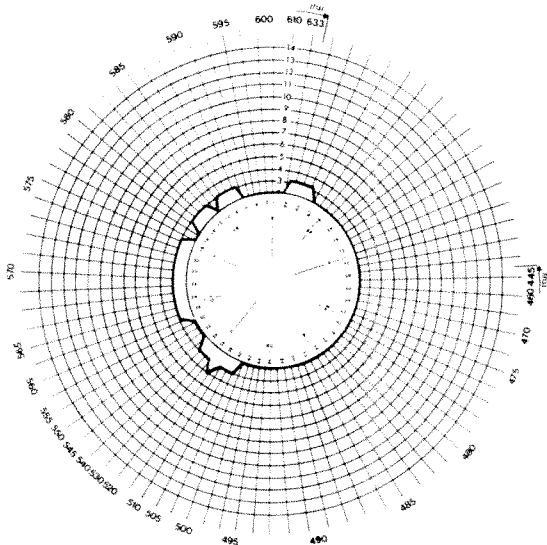


Fig. 4 Case V₄. Normal Farnsworth-Munsell 100 hue test.

abnormal VER with symmetrically delayed P2 latencies outside the normal range (P2 latency 136 ms in each eye; normal range 90-131 ms). The ophthalmoscopic appearance in each case was considered normal.

The 3 children (cases V₈, V₉, V₁₁, ages 17-12 years) of case IV₅ were also found to have abnormal colour vision on the F-M test, with increased error

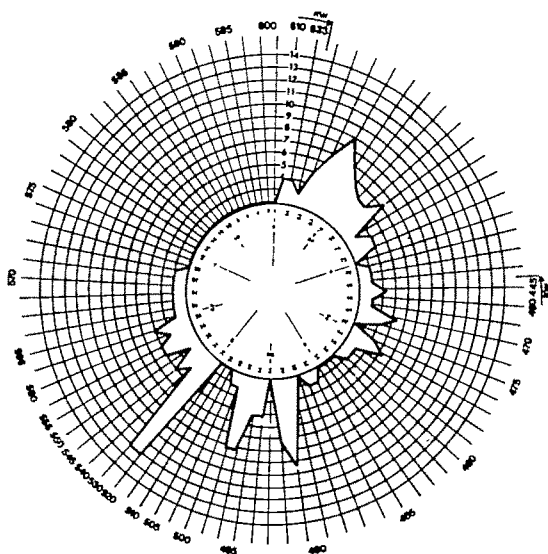


Fig. 5 Case V_1 . Farnsworth-Munsell 100 hue test demonstrating increased total error score with maximal error in the red-green axis.

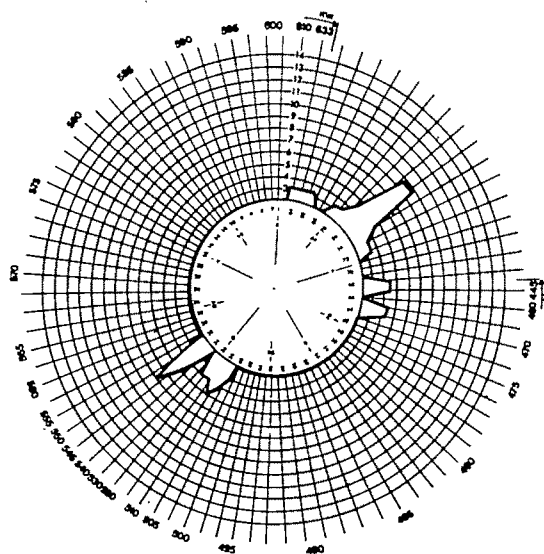


Fig. 6 Case V_1 . Farnsworth-Munsell 100 hue test with normal total error score but with maximal error in the red-green axis.

scores in each instance and a pattern of generalised poor colour discrimination (Fig. 7). The AQ of 1.247 in case V_8 was abnormal, showing a green deficient match. The youngest daughter (case V_{11}) had bilateral temporal disc pallor, while the ophthalmoscopic appearances in her siblings were normal. The visual fields and VERs were normal in each case.

Case IV_7 , who was an unaffected male, and his 2 children (ages 6 and 9 years) had normal ophthalmoscopic appearances and VERs, but the children were too young to co-operate fully with the F-M and anomaloscope tests.

Discussion

SYMPTOMATIC INDIVIDUALS

The clinical neuro-ophthalmological and VER findings in the 2 affected patients reflect the state of advanced optic atrophy with markedly decreased visual acuities, flat unrecognisable VERs, central scotomata, and dyschromatopsia. The onset and progression of visual failure in these 2 cases is typical of Leber's optic neuropathy, and the appearance of the disc recorded at the time of onset of the symptoms is similar to that reported by others in the acute phase of the disease.^{14 15}

ASYMPTOMATIC INDIVIDUALS

In keeping with the expected pattern of genetic transmission no abnormalities were detected in

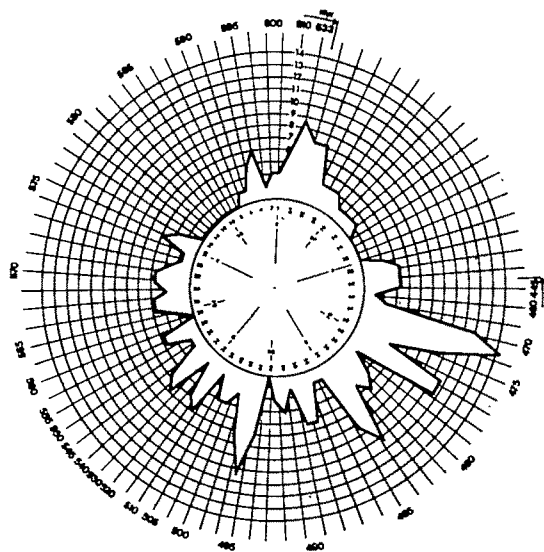


Fig. 7 Case V_8 . Abnormal Farnsworth-Munsell 100 hue test with increased total error score and a pattern of generalised poor discrimination.

children of either affected or unaffected males in this pedigree. In contrast, however, abnormalities of colour vision, disc appearances, and/or VER in some asymptomatic potential or obligate female carriers and males at risk suggest that carrier detection and preclinical diagnosis is possible in

Leber's optic neuropathy. The significance of increased retinal small vessel tortuosity observed in case III₂, an obligate female carrier, is uncertain but has been noted previously in clinically affected patients^{14,15} and in some asymptomatic family members.¹⁰ It has been suggested that this increased tortuosity of small blood vessels is a separately inherited trait,¹⁶ but this requires further study. The assessment of temporal pallor of the optic discs is notoriously unreliable. The disc appearance of temporal pallor in case IV₁₁ was noted by 2 independent clinicians, and this, together with the abnormal colour vision, to the best of our knowledge, represents the youngest asymptomatic member of a Leber's family to show neuro-ophthalmological abnormalities.

The abnormalities noted on colour testing require further analysis. Ishihara pseudoisochromatic plates provide a rapid method of detecting congenital colour deficiency but are less sensitive in determining acquired dyschromatopsia than tests such as the F-M 100 hue test.^{12,17} Impairment of colour vision is a sensitive index of damage to the optic nerve,¹⁸ and recent studies have emphasised the accuracy of the F-M 100 hue test in detecting acquired colour vision defects in optic nerve disease.^{17,19} The greater sensitivity of the F-M hue test is evident in this study. Of the 6 asymptomatic patients who had total error scores outside the normal range for their respective ages only 2 made mistakes on reading the Ishihara plates (cases III₂ and V₁).

The nature of the defective colour discrimination is of interest. In those patients in whom a confusion axis is recognisable on the polar co-ordinate diagram of the F-M 100 hue test, the axis is noted to lie in the red-green plane. Acquired red-green deficiency has been noted in most diseases of the optic nerve, including Leber's optic neuropathy, and is characterised by a deutan-like discrimination defect.¹² The abnormalities on the F-M 100 hue test were further confirmed by the anomaloscope, which tests the patient's ability to achieve Rayleigh's match. This match was noted to be deuteranomalous (green deficient) in all the patients with abnormal total error scores in the F-M test. In addition 1 patient (V₂) who had a normal error score but a clear red-green axis on the 100 hue test had a green-deficient match on the anomaloscope. These findings correspond to the deuteranomalous match of acquired red-green deficiency occurring with diseases of the optic nerve.¹²

The finding of a red-green axis on the F-M 100 hue test with a normal anomaly quotient is difficult to interpret in case IV₅, a potential carrier. The findings of abnormalities in all her children suggest that she is a detectable carrier of Leber's optic

neuropathy. The significance of the abnormalities in her children will have to be clarified with the passage of time. Her son (case V₃) is clearly at risk for developing the disease, while his sisters, though at risk for developing the disease, are more likely to remain asymptomatic carriers.

The finding of symmetrically delayed VER P2 latencies in a young male at risk (case V₂) suggests presymptomatic or early optic neuropathy. Similarly his brother, case V₁, although having normal VERs, must be placed in the high risk category in view of his abnormal colour discrimination. The abnormalities of colour vision noted in their mother, a potential carrier, further increase their risk of developing the disease. The predictive value of these investigations will have to be confirmed over the following few years, when these patients are likely to become symptomatic.

The finding in the present study of neuro-ophthalmological abnormalities in the daughters of female carriers in this family but not in the offspring of affected and unaffected males supports Seedorf's estimate²⁰ of a high carrier rate approaching 100% in daughters of carriers of this disease.

Although there is no conclusive proof of a metabolic viral or toxic cause for Leber's optic neuropathy, reports have suggested a defect in cyanide metabolism in this disorder.²¹ The detection of presymptomatic cases of Leber's optic neuropathy naturally raises the question of prophylactic treatment. No treatment has yet been shown to be effective in symptomatic cases of this disorder. Nikoskelainen *et al.*¹⁵ unsuccessfully treated 2 affected brothers in the early phases of the disease with prednisone and hydroxycobalamin. In view of the suspected defect in cyanide metabolism in some of these cases we think it advisable to give the 2 presymptomatic patients in our study high doses of hydroxycobalamin. This treatment is without side effect and appears to be the only therapeutic option available at this stage of the disease.

Our findings of neuro-ophthalmic abnormalities in some asymptomatic members of a family with Leber's optic neuropathy support those of a previous study¹⁰ and indicate that acquired dyschromatopsia, best detected by the F-M 100 hue test, may be the only detectable sign of optic nerve dysfunction. The predictive value of these neuro-ophthalmological abnormalities will, however, have to be confirmed by serial examinations over the next few years.

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Treatment of acute retrolental fibroplasia by cryopexy

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SUMMARY Fifteen to 20% of premature infants weighing below 1500 g develop variable degrees of acute retrolental fibroplasia (RLF). Approximately 5% of those infants who develop RLF can be expected to become blind. A prospective study was carried out to evaluate if early cryopexy can prevent this blindness. The study showed that, among 533 infants admitted to the neonatal intensive care unit between July 1976 and December 1978, 55 had some degree of active RLF. In 18 eyes of 9 infants in whom the retinopathy progressed beyond active stage II cryopexy treatment was applied to the avascular retina. In all the treated eyes the active retinopathy regressed, and there were no complications due to the procedure. The long-term follow-up showed that in 15 eyes there was good vision and that the remaining 3 eyes had some impairment of vision but were not blind. These results suggest that cryotherapy may prove useful in treating premature infants with RLF who show progression of their active stage, without the danger of further visual loss or complete blindness.

Retrolental fibroplasia (RLF) is still a persistent problem in spite of modern techniques of monitoring Pao_2 levels. Since both the incidence and the severity of RLF are directly related to the degree of prematurity as manifested by low birthweight (see Tables 1, 2), this disorder can be expected to become an even more serious problem with the increasing capability of preserving life in extremely small premature infants.

In the majority of infants with RLF there is a spontaneous regression of the active stages with a subsequent normal vision. It has been found, however, that about 5% will become totally blind due to cicatricial RLF (Table 2). In addition, a certain number, as yet undetermined, will show other serious ocular abnormalities such as high myopia, vitreous traction, dragged retinal vessels, heterotopic macula, strabismus, and amblyopia. Late complications include peripheral retinal degeneration, retinoschisis, retinal tears, and retinal detachment.

Several authors¹⁻³ have worked out grading systems for the classification of the various stages of acute and cicatricial RLF. Others⁴ have provided more understanding of the pathogenesis of the disease by their report on the use of fluorescein

angiography and the clinicopathological correlations derived from it. There are, however, only a few recent reports on the incidence, prevalence, and natural history of this disease, especially in premature babies with RLF weighing below 1500 g at birth.

Since RLF has characteristics which are common to other ischaemic retinopathies, it was only natural that methods of treating such retinopathies, such as photocoagulation and cryopexy, would be tried in its treatment as well. Conflicting results have been obtained by this approach,⁵⁻¹² probably owing to the lack of clear indications as to the optimal time of treatment and the exact method to be used.

In July 1976 a prospective study was started on premature babies with acute RLF to see whether blindness could be prevented by giving cryopexy treatment to selected eyes judged to have an increased probability of developing severe cicatricial RLF. The results of Kingham's series¹² encouraged us to report the preliminary results of this study even before data from controlled studies on large numbers of eyes are available, in order to demonstrate that cryopexy, if done early, may be not only harmless but better than no treatment or than treatment carried out only when the eyes reach active stage IV, as in Kingham's series.¹² The purpose of this report is also to stress the direct relationship between low birth weight and the

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Table 1 Incidence of active retrolental fibroplasia and birthweight

Reference	Total no. preterm infants	% with acute RLF	Birth weight (in grams)			
			500-1000 No. of RLF	1001-1500 No. of RLF	1501-2000 No. of RLF	2001-2500 No. of RLF
Kinsey <i>et al.</i> ¹⁴	719	10.6%	—	86 (36%)		
Johnson <i>et al.</i> ¹²	176	18%	8 (75%)	50 (32%)	52 (17%)	37 (5%)
Kingham ⁸	521	16%	Not reported			
Majima ¹⁷	470	32.6%	Not reported			
Present study	533	10%	31 (61%)	112 (20.5%)	209 (5.2%)	68 (1.5%)

Table 2 Severity of cicatricial RLF in relation to birth weight in previous studies

Reference	Total no. infants	No. of infants with active RLF	No. of eyes with cicatricial RLF from total infants	No. of eyes with cicatricial RLF grades I-II from infants with active RLF	Same for grade III	Same for grades IV-V	Infants below 1000 g	No. of eyes with cicatricial RLF from all infants below 1000 g	Comments
Kinsey <i>et al.</i> ¹⁴	719	66 (11%)**	27 (4%)	21 (32%)	3 (5%)	3 (5%)	86*	34 (20%)* 17 (20%)	*Under 1200 g birthweight. **10 cases excluded because of lack of data. 1971
Gunn <i>et al.</i> ¹⁵	?	?	—	24 (34%)	2 (3%)	4 (11%) 4 (6%)	18 35	4 (11%) 15 (43%)	Data from 1962-71. Data from 1972-6
Lempert ¹⁶	185	8 (5%)	17 (5%)	12 (33%)*		5 (14%)*	—		*Estimate based on 10% active RLF 1975
Johnson <i>et al.</i> ¹²	176	33 (19%)		19 (29%)		2 (3%)	8		1968-71
Shahinian and Malachowsky ¹³	375	12 (3%)	8 (11%)			8 (11%)*			*Estimate based on 10% active RLF 1973-4

occurrence and severity of RLF, the absence of long-term complications due to the treatment, and the absence of any blindness in the treated eyes.

Materials and methods

All of the 533 surviving premature babies admitted to the neonatal Intensive Care Unit of the Beilinson Medical Center between July 1976 and December 1978 were examined. The first indirect ophthalmoscopic examination was usually carried out at the age of 2 weeks, with a subsequent monthly examination up to the age of 6 months. Acute retrolental fibroplasia was diagnosed in 55 infants (10%), who were then examined weekly. Eyes were considered to require treatment if serial examinations revealed progression of the retinopathy beyond active stage II according to Patz's classification.³ In the initial stages of this study only the worse eye was treated. However, 2-6 weeks later, when it was evident that there was an arrest of the active retinopathy in the treated eye and that no

complication had occurred, the fellow eye was treated too, if it had also progressed beyond active stage II.

Cryopexy was performed under general anaesthesia with ketamine hydrochloride, with or without the use of an endotracheal tube. The conjunctiva was never incised and the muscles were never held by fixation forceps or fixation sutures. Under observation with an indirect ophthalmoscope a retinal cryoprobe was placed transconjunctivally over the peripheral avascular retina. The retina anterior to the neovascularisation tufts was treated, each location being frozen only once. No particular attempt was made to freeze the neovascular tufts themselves. No special postoperative treatment was applied.

Results

Among the 55 infants with active RLF the retinopathy never exceeded stage II in 46 (84%), and eventually spontaneously regressed and healed. All

the 9 infants in whom the active retinopathy started to progress beyond stage II and who were subjected to treatment weighed below 1500 g at birth. Three weighed between 1001 and 1500 and 6 weighed between 500 and 1000 g (Table 3). In these infants the temporal ridge was thick, and the neovascular

tufts were large and engorged. There was an elevated retinal neovascularisation and small to moderate vitreous haemorrhages. After ablative cryopexy over the avascular retina these 18 eyes showed a rapid arrest of the active retinopathy and started to heal.

No complications resulted from the cryoapplication. In all cases the slight conjunctival chemosis and lid swelling present postoperatively subsided within 2-3 days. None of the eyes progressed to more than cicatricial stage II. Fifteen of these treated eyes were later found to have macular fixation, and they were considered to have good vision. Of the other 3 eyes, 1 became highly myopic (case 7, Table 4) and 2 developed mildly displaced macula (case 1, Table 4).

Discussion

Only a few published reports provide precise data of the natural history of acute RLF (Table 2). It is generally accepted that the mild forms of RLF are reversible. It was noted in previous studies, as well as in ours, that the great majority of cases of acute RLF occur among infants of low birth weight, and that they are more severe.^{13,14}

Table 3 Incidence and severity of active RLF in relation to birthweight

Birthweight in g	No. of infants	Infants with acute RLF	Active RLF exceeding stage II treated cases	% of active RLF treated % of total no. of infants
500-1000	31	19 (61.3%)	6	$\frac{32\%}{19\%}$
1001-1500	112	23 (20.5%)	3	$\frac{13\%}{3\%}$
1501-2000	209	11 (5.2%)	—	—
2001-2500	68	1 (1.5%)	—	—
2500-	113	1 (0.9%)	—	—
Total	533	55 (10.3%)	9	$\frac{16\%}{1.6\%}$

Table 4 Relevant data on 18 eyes with retrolental fibroplasia

Case	Eye	Birth weight (g)	Days in oxygen	Max. Pao ₂	Age at diagnosis (weeks)	Shape of active RLF at diagnosis	Age at treatment (weeks)	Optic nerve angle*	Active RLF stage at treatment	Duration of follow-up	RLF stage cicatricial	Optic nerve angle	Comments	Ocular picture at last examination
1	OD OS	800	4	120	7	II II	9 11	100° 75°	III III	72 weeks	II II	70° 55°	Good vision 4.5 sph. myop.	Displaced macula Displaced macula Esotropia
2	OD OS	620	7	55	10	I I	13 15	120° 120°	II III	63	I I-II	100° 90°	Good vision Good vision	Normal Opaque mass in periphery
3	OD OS	1080	8	64	12	I I	15 16	120° 120°	II-III II-III	45	— —	120° 120°	Good vision Good vision	Normal Normal
4	OD OS	980	7	170	6	I I	10	100° 100°	III-IV III-IV	41	I-II I	100° 110°	Impaired vision Good vision	Macular changes Normal macula
5	OD OS	750	1	66	10	I I	13 12	90° 90°	II+ III	34	I I	100° 100°	Good vision Good vision	Good macula Good macula
6	OD OS	1140	1	130	3	II I	9 7	100° 100°	III III	30	— —	110° 110°	Good vision Good vision	Good macula Good macula
7	OD OS	900	3	79	7	I I	16 16	100° 100°	II-III II-III	30	I I	100° 100°	Good vision 9.0 sph. myop.	Good macula Good macula
8	OD OS	1430	30	185	6	I I	9 9	120° 120°	II-III II-III	28	I I	120° 120°	Good vision Good vision	Good macula Good macula
9	OD OS	880	1	88	8	I I	15 15	120° 120°	II-III II-III	20	— —	120° 120°	Good vision Good vision	Good macula Good macula

OU = both eyes, OD = right eye, OS = left eye. *Angle of main blood vessels emerging from the optic disc.

Among the 533 premature infants studied by us there was an inverse relationship between the birth weight of the infant and the prevalence of acute RLF (see Table 4). It is of note that in the group of premature babies with a birth weight under 1000 g the prevalence of acute RLF was between 61 and 75% (Table 1), and generally the RLF changes were more advanced than in premature babies with RLF with birth weight above 1000 g.

Few statistics have been reported on the results of cryopexy treatment. In the co-operative 5-year study on the natural history of RLF,¹⁴ which involved 5 central intensive neonatal care units, there were 66 infants with acute RLF, of whom 32 were between 1000 and 1200 g birth weight. Of these, 3 became blind due to grades IV and V cicatricial RLF, and 3 had grade III cicatricial RLF, both stages being compatible either with low vision or with legal blindness. Of the 35 premature babies weighing 500–1000 g at birth who were followed up at the Montreal Children's Hospital by Gunn *et al.*¹⁵ 15 (43%) had cicatricial RLF; of these, 6 (20%) children were blind, 10 other children (28%) had high myopia, and 2 more had esotropia.

Since our findings, as well as those of other workers, indicate that the prevalence and severity of RLF are positively related to the degree of retinal prematurity, or in other words to the extent of the zone of avascular hypoxic retinal tissue, it may be assumed that the development of RLF is triggered, as are other ischaemic retinopathies, by a vasoformative substance produced in the ischaemic retina. The larger the stimulus in the area of the available ischaemic retina to produce this substance, the greater would be the vasoproliferation, and hence the greater would be the chance for occurrence of complications leading to cicatricial forms. As in other ischaemic retinopathies, destruction of ischaemic retina is believed to reduce the formation of vasoformative substance and consequently to cause an arrest of the disease.

Our results suggest that such a destruction is easily achieved with cryopexy. In each of the treated eyes there was a rapid resolution or regression of the acute RLF changes. We decided to treat the second eye when it was observed that during the 2–6 weeks of the follow-up period the untreated eye continued to deteriorate, while the previously treated eye showed good regression of the acute RLF.

No complications were encountered which could be attributed to the cryopexy. These findings are unlike those of Kingham,¹² who, in an unrandomised treatment study, reported optic atrophy and severe forms of cicatricial retinopathy after cryo-application. These different results may be attributed to the differences in the time of treatment,

to the surgical technique, and to the location of the cryoapplications. In our mode of treatment we did not attempt to destroy directly the ridge or the neovascular fronds themselves, but applied the cryoprobe only to the avascular peripheral retina, an approach which did not necessitate incising the conjunctiva, pulling muscles, and applying an inevitably stronger pressure on the premature eye. Since we treated the peripheral avascular retina while it was still close to the choroid and not already highly detached, we were able to freeze it properly and by less extensive applications. When the retina is already highly detached, heavy cryoapplication over the sclera and choroid may increase leakage from the choroidal vessels and thus increase the exudative detachment.

In Kingham's report¹² from a series of 101 premature babies of various birth weights, of whom 14 eyes were treated, there was 7% of blindness. We feel that if treatment is performed earlier the rate of blindness should be less, because the acute RLF does not progress to stage IV, a stage in which the chance of successful treatment is, as previously explained, smaller. For the later stages of active, as well as for cicatricial RLF, surgery with an external buckling procedure may be the best solution.¹⁶

In light of the above findings it is encouraging to report that in our preliminary treatment study there was not a single case of blindness among the 55 children with acute RLF, of whom 32 had a birth weight below 1000 g, and none progressed beyond active stage III. These results indicate that cryotherapy used in the method described here is safe and effective in arresting acute RLF and in preventing the progress of the retinopathy towards the severe forms of active and hence cicatricial RLF. The question which remains open is which of the treated children would have had their disease spontaneously regress if left untreated. Since all the children were treated before they reached active stage IV, unlike those in Kingham's series, it is impossible to provide an answer to this question until better criteria for prediction are available.

We thank Dr S. Reisner, head of the Neonatal Unit, and Dr R. Krickler for their excellent co-operation during the study.

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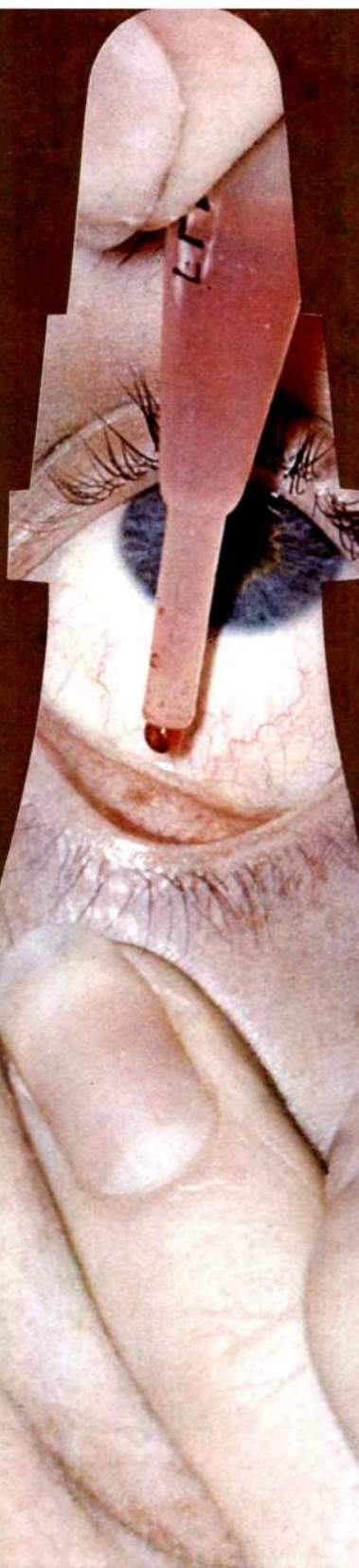
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A comparison of acyclovir and idoxuridine as treatment for ulcerative herpetic keratitis

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SUMMARY Sixty patients were treated with either acyclovir 3% ointment or idoxuridine 1% ointment 5 times a day in a stratified randomised double-blind clinical trial. The 2 antiviral agents were equally effective.

Acyclovir (ACV, previously called Wellcome 248U and acycloguanosine) is a compound active in herpes simplex virus (HSV) infections. It has considerable clinical potential because it is extremely specific. Only cells infected with virus, and therefore with virus-coded thymidine kinase, phosphorylate the drug to a form capable of inhibiting DNA-polymerase. Furthermore, it does not appear to be metabolised to inactive substances by human cells.¹ The inhibition of viral coded DNA-polymerase is also highly specific. The potential value of the drug is related to its high specificity and low toxicity. Acyclovir has been demonstrated to possess potent antiviral activity in vitro and in animal models of herpetic keratitis.²

Clinical studies have confirmed the activity of the drug in human herpetic disease. The first of these studies involved debriding epithelial lesions produced by HSV and comparing the ability of acyclovir to prevent lesion formation.³ When dendritic ulcers are treated with debridement alone, healing is rapid and patients become free of pain within 24-48 hours. However, 50% of patients so treated develop small foci of viral activity in the epithelium within a week of treatment that requires further debridement or antiviral chemotherapy.⁴ Placebo-controlled trials designed to test an antiviral agent's ability to suppress the formation of these microscopic lesions are capable of demonstrating a potentially useful biological activity while subjecting a very small number of patients to a small amount of drug.

The biological activity of acyclovir having been confirmed in human viral disease, the next step was to compare the drug used in a more conventional manner to established antiviral chemotherapy. Here we report the results of a trial comparing the effects of acyclovir and idoxuridine (IDU) ointments on the rate of healing of herpetic corneal ulcers.

Patients and methods

Sixty consenting patients presenting with ulcerative herpetic keratitis were admitted to the trial. Patients were allocated to strata on the basis of clinical features likely to be significant in prognosis. The stratification factors were the type of ulcer, that is, geographic or dendritic, the size of the ulcer, whether the patient had received topical corticosteroids within the 3 weeks prior to presentation, and the degree of inflammatory reaction in the cornea and anterior chamber. Within these strata patients were randomly allocated to 1 of 2 treatment groups. One group received IDU 1% ointment 5 times a day until the epithelial defect had healed and then 3 times a day for 3 more days. The other group received acyclovir 3% ointment 5 times a day until the epithelial defect healed and then 3 times a day for a further 3 days. All patients received a drop of atropine 1% each day until healed. Neither the patient nor the ophthalmologist knew which treatment was being used, so that the trial was stratified, randomised, and double-blind.

Having begun treatment, patients were examined at the slit-lamp on alternate days. The point of healing was judged to have occurred when no epithelial defect was demonstrable with rose Bengal and fluorescein staining.

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Results

Sixty patients were admitted to the trial. Fifty-four had dendritic and 6 had geographic (amoeboid) ulcers. Thirty received IDU and 30 received acyclovir. The distribution of patients is set out in Table 1. One patient treated with acyclovir failed to present regularly for follow-up, though he responded favourably in that his geographic ulcer had healed when he returned 10 days after beginning therapy. He is not included in the analysis.

There were no treatment failures, nor were there any untoward reactions that necessitated withdrawal of therapy. One patient developed an allergic reaction that subsided on withdrawing the atropine drops.

The results were evaluated on the basis of the number of days it took the ulcers to heal in each group. The distribution of healing times for patients in both treatment groups is set out in Fig. 1. A cumulative frequency curve indicating the pattern of healing in each group is displayed in Fig. 2. Clearly the patterns are very similar, and a logrank analysis indicates that the difference between the

curves is likely to have occurred by chance ($P > 0.05$). When the geographic ulcers are excluded from the analysis the difference between the groups is even less (Fig. 3).

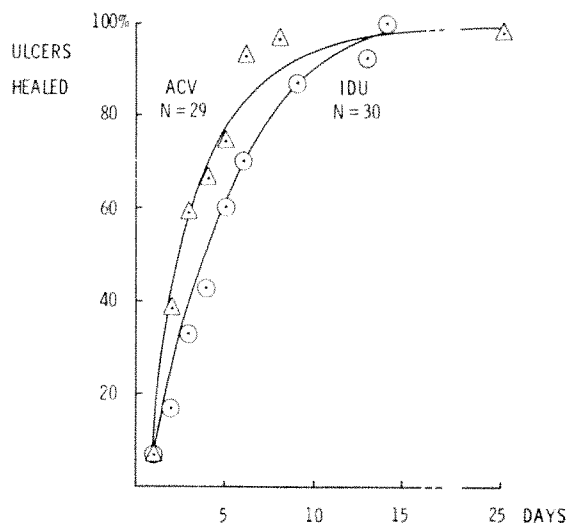


Fig. 2 Cumulative frequency graph of the time taken to heal of 59 herpetic corneal ulcers (54 dendritic, 5 geographic) treated with acyclovir (ACV) or 5-iodo-2' deoxyuridine (IDU).

Table 1 Distribution of patients with dendritic or geographic ulcers to treatment group to receive idoxuridine (IDU) or acyclovir (ACV)

	IDU	ACV
Geographic	4	2*
Small dendritic	14*	14*
Large dendritic	12	14
Total	30	30

*Patients with marked inflammatory reaction in the corneal stroma and anterior chamber.

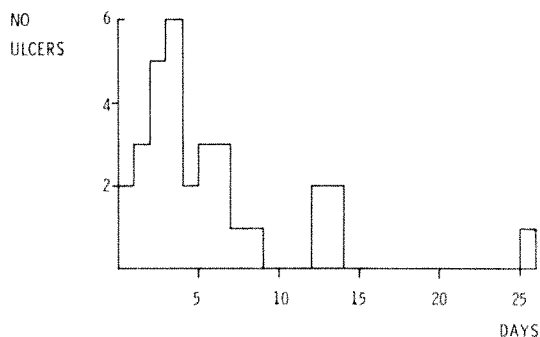


Fig. 1 Histogram of healing times of herpetic ulcers treated with acyclovir (ACV) and 5-iodo-2' deoxyuridine (IDU).

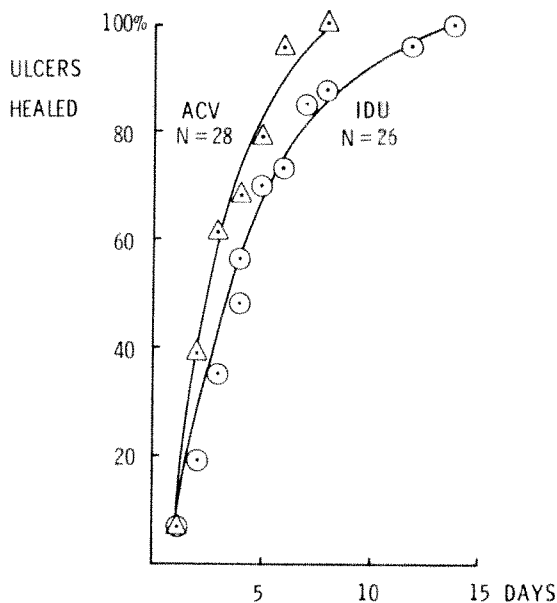


Fig. 3 Cumulative frequency graph of the time taken to heal of 54 dendritic ulcers treated with acyclovir (ACV) or 5-iodo-2' deoxyuridine (IDU).

Discussion

The results of this trial establish that acyclovir is an effective antiviral agent for treating ulcerative herpetic keratitis, since it is at least as active as IDU.

It is to be expected that such a trial will yield a null result. The majority of ulcers are dendritic rather than geographic. IDU is so effective for dendritic ulcers, with 100% of patients being healed within 14 days, that there is little chance of another antiviral agent bringing about a significant improvement on what is achieved with IDU. This is not to say that a null result is insignificant, but it demands that trials be well designed, carefully conducted, and the data be analysed in an appropriate manner.

A further limitation of trials evaluating antiviral agents as treatment for dendritic ulcers is that they do not provide any information on chronic toxicity, as the majority of patients complete the treatment programme in less than 2 weeks. This is a major limitation, since it is the toxicity of antivirals that limits their clinical usefulness.

Since it is established that acyclovir is as effective as IDU in the treatment of ulcerative herpetic keratitis, the next step is to evaluate the drug in situations in which currently employed therapeutic measures are less than universally satisfactory. Geographic ulcers are generally more difficult to treat than dendritic ulcers. They have been shown

to represent a different level of challenge and are capable of demonstrating a difference between antiviral agents that cannot be appreciated when only dendritic ulcers are studied.⁶ Herpetic corneal ulcers which have failed to heal with IDU or debridement are another difficult problem with which to challenge a prospective new topical antiviral agent. Stromal keratitis is also a form of herpetic eye disease often resistant to current therapy. An important challenge is to conduct trials directed at evaluating this new antiviral agent in these sight-threatening conditions. Because of its remarkably low toxicity and high specificity, acyclovir is a drug with exciting therapeutic potential.

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Randomised double-blind trial of acyclovir and idoxuridine in dendritic corneal ulceration

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SUMMARY The results of a randomised double-blind clinical trial of 3% acyclovir and 0.5% idoxuridine (IDU) ophthalmic ointments in 60 patients with corneal dendritic ulceration are presented. Ulcers in all 30 patients treated with acyclovir healed compared with 22 (76%) of 29 patients treated with IDU ($P < 0.01$). Patients treated with acyclovir healed more rapidly (average 4.4 days) than those who received IDU (average 9.2 days) ($P < 0.01$). No serious side effects were observed, though transient stinging was recorded in 8 patients receiving acyclovir and in 2 patients receiving IDU. Other side effects in the IDU treated group were watering in 2 patients and superficial punctate erosions in 6 patients.

Idoxuridine (IDU) has been used for the treatment of herpes simplex keratitis since 1962,¹ and its efficacy in treating this infection has been established. Results from controlled trials indicate an average cure rate of 76%.²⁻¹⁰ However, the drug is known to produce toxic effects, including follicular conjunctivitis, contact dermatitis, epithelial keratitis, and occlusion of the punctum.¹¹ More effective and less toxic alternatives have been sought. Adenine arabinoside (ara-A) has a similar level of efficacy to IDU,⁶ while trifluorothymidine (F3TDR) is somewhat more effective.¹²

Acyclovir (Zovirax, 9-(2-hydroxyethoxymethyl)guanine) was developed by Elion, Schaeffer, and Bauer.^{13,14} In vitro acyclovir is over 10 times more active against herpes simplex virus (HSV) type 1 than either IDU or F3TDR. The first step in the phosphorylation of acyclovir to the active triphosphate is carried out by viral specified thymidine kinase. Acyclovir triphosphate inhibits HSV DNA polymerase 10-30 times more effectively than cellular DNA polymerase, resulting in preferential inhibition of viral DNA synthesis.

Acyclovir has been shown to be superior to IDU in the treatment of experimental corneal infections with HSV in the rabbit¹⁵ and has also shown promise in treating dendritic ulceration in man. In patients treated with minimal wipe debridement Jones *et al.*¹⁶ showed that topical treatment with acyclovir prevented early recurrences in comparison with placebo.

Recently acyclovir was shown to be effective without debridement in treating a series of patients with dendritic ulceration, a proportion of whom had failed to respond to other antiviral agents.¹⁷ This report describes the results of a randomised double-blind controlled trial of acyclovir and IDU ophthalmic ointments in patients with superficial corneal ulceration.

Materials and methods

Sixty patients were included in the study. Informed consent to participation in the investigation was obtained from patients or parents as appropriate. Uniocular patients and those who had received local antiviral treatment or steroids during the preceding 2 months were excluded. Diagnosis was based on clinical criteria; full ocular examinations were carried out initially and during the follow-up assessments. Patients were examined as often as clinically necessary, but all were seen at least twice weekly. Conjunctival swabs were taken for virus culture, and sera were collected for titration of complement fixing (CF) antibodies to herpes simplex virus (HSV). Treatment 5 times daily with either 3% acyclovir or 0.5% IDU ophthalmic ointments was randomly allocated. The ointments were of similar appearance and packed in identical tubes. In addition all patients received 1% homatropine eye drops twice daily and the infected eyes were padded. If no improvement had occurred after 4 days' treatment, the patient was withdrawn from the study and treated with 3% ara-A ophthalmic oint-

ment. Ulcers were considered to have healed when there was no fluorescein uptake, and the day of healing was noted. Symptoms of pain, photophobia, lachrymation, and grittiness were scored at each visit on a four point scale (0—absent, 1—mild, 2—moderate, 3—severe).

VIROLOGY

Conjunctival swabs were placed in virus transport medium immediately after collection. As soon as possible thereafter 0.2 ml of the transport medium was inoculated into available cell cultures. The cultures in routine use were Vero, HeLa, primary African green monkey kidney, and human embryo lung (HEL) fibroblasts. Specimens were considered positive if they produced cytopathic effects (CPE) in HEL fibroblasts and one or more of the other cell cultures, and negative if they failed to produce CPE in HEL fibroblasts and at least 2 other cell types. Virus isolates were identified by neutralisation with antisera supplied by the standards laboratory for Serological Reagents, Public Health Laboratory Service, Colindale. Sera were titrated for CF antibody to HSV type I by standard methods.

Results

Thirty patients were entered into each group; 1 patient in the IDU treated group failed to attend

Table 1 Comparison of acyclovir and IDU treated groups at presentation

	Acyclovir	IDU
Number of patients treated	30	30*
Number (%) female	11 (36.7%)	5 (16.7%)
Age range (yr)	4–79	18–62
Average age (yr)	39	43
Duration of symptoms before treatment		
<2 weeks	22 patients	24 patients
2–4 weeks	8 patients	3 patients
>4 weeks	0 patients	3 patients
Average severity of symptoms at presentation (range 0–3)		
Pain	1.6	1.5
Photophobia	1.3	1.7
Lachrymation	1.5	1.9
Grittiness	1.4	1.4
Approximate ulcer size at presentation		
Range	1–36 mm ²	1–49 mm ²
Average	8.3 mm ²	8.3 mm ²
Number of patients with uveitis	5	3†

*One patient failed to attend for follow-up. †Two additional patients developed uveitis during treatment.

for follow-up. The 2 groups of patients were similar with regard to sex and age distributions, duration and severity of symptoms before treatment, occurrence of uveitis, and size of corneal ulcers (Table 1). Herpes simplex virus type I was recovered from 19 (33%) of 54 conjunctival swabs. CF antibody to HSV type I was present in 48 (96%) of sera. There were no differences in the rate of recovery of HSV or in the percentage of patients with CF antibody between the 2 groups.

All ulcers treated with acyclovir healed, while ulcers in 7 (24.1%) of 29 patients were not improved or had become worse after 4 days' treatment with IDU ($P < 0.01$, Cox's logit procedure). These patients were withdrawn from the study. The number of days taken to heal in patients treated with acyclovir ranged from 2 to 9 days (average 4.4 days), compared with 3 to 17 days (average 9.2 days) for patients treated with IDU (Tables 2 and 3).

Table 2 Thirty patients treated with acyclovir

Patient sex, age (yr)	Number of days to healing	Side effects	Recovery of HSV from conjunctival swabs	Titre of complement fixing antibody to HSV	Follow-up period (months)
M48	4	Nil	—	1/16	13
M58	4	Nil	—	1/64	13
M12	4	Nil	+	1/256	13
M53	4	Nil	—	1/32	13
F54	3	Stinging	—	1/32	12
M70	4	Sore tongue	—	1/32	12
M40	3	Nil	—	1/32	12
F58	5	Nil	+	1/16	11
M55	6	Nil	—	1/16	11
F4	9	Stinging	+	ND	10
M37	4	Nil	+	1/16	10
M62	3	Stinging	—	1/8	10
M35	4	Nil	+	1/32	10
F22	4	Nil	+	1/16	10
F22	4	Stinging	+	1/16	9
M79	5	Nil	+	1/32	9
F11	7	Nil	ND	ND	8
M23	6	Nil	+	ND	8
F12	4	Stinging	—	1/64	8
F73	5	Stinging	—	1/32	8
M41	5	Nil	—	1/32	7
F12	2	Nil	—	1/32	7
M57	3	Stinging	—	1/32	6
M25	4	Nil	—	1/32	6
F26	5	Nil	ND	ND	5
M42	4	Nil	—	1/32	4
M8	4	Nil	—	ND	4
M52	3*	Nil	—	1/32	4
M49	3	Nil	—	1/32	4
F26	6	Stinging	—	1/32	2‡

ND = Not done. *Recurred after 3 weeks.

Table 3 *Thirty patients treated with IDU*

Patient sex, age (yr)	Number of days to healing	Side effects	Recovery of HSV from conjunctival swabs	Titre of complement fixing antibody to HSV	Follow-up period (months)
M51	7	Nil	—	1/32	13
M55	8	SPE	—	1/32	13
M52	10	Nil	—	1/32	13
M50	9	SPE	ND	ND	12
M34	Withdrawn	—	—	1/64	—
M61	8	Nil	+	1/32	11
F47	Withdrawn	—	ND	ND	—
F41	10*	Irritation	—	1/64	11
M60	Defaulted	—	—	1/32	—
M40	11	Nil	—	1/32	11
M34	7	Nil	—	1/16	10
M25	10	SPE	—	1/64	10
M40	7	SPE	+	1/32	10
M35	8†	Stinging	—	1/8	10
M60	8	Nil	—	1/16	10
M40	8	Nil	—	1/16	10
M18	8	Nil	—	1/16	9
F49	8	Nil	—	1/32	9
M49	Withdrawn	—	ND	ND	—
M24	Withdrawn	—	—	1/8	—
F50	10	Nil	—	1/32	7
F62	Withdrawn	—	ND	ND	—
M40	11	Nil	—	1/32	6
M40	Withdrawn	—	—	1/32	—
M48	17	SPE	—	1/32	6
M23	3	SPE	—	1/32	4
M27	7	Watering	—	1/32	4
M56	Withdrawn	—	+	1/8	—
M22	10	Watering	—	1/64	3
M58	6	Nil	—	1/64	3

ND = Not done, SPE = Superficial punctate erosion, *Recurred after 8 weeks, †Recurred after 4 months.

The cumulative rate of healing for both treatments is given in Fig. 1. The difference between the 2 groups in terms of healing rate was significant ($P < 0.01$, log rank analysis). Two of 30 patients treated with acyclovir and 20 of 29 patients treated with IDU took more than 6 days to heal.

Five patients presented with uveitis in the group treated with acyclovir, which resolved in 3–11 days (average 7 days). Uveitis was present in 3 patients treated with IDU and developed during treatment in a further 2. Two patients were withdrawn from the study, while the other 3 resolved, respectively in 2, 7, and 23 days.

Symptoms of pain, photophobia, lachrymation, and grittiness resolved within 11 days in all except 4 patients—all of whom were treated with IDU.

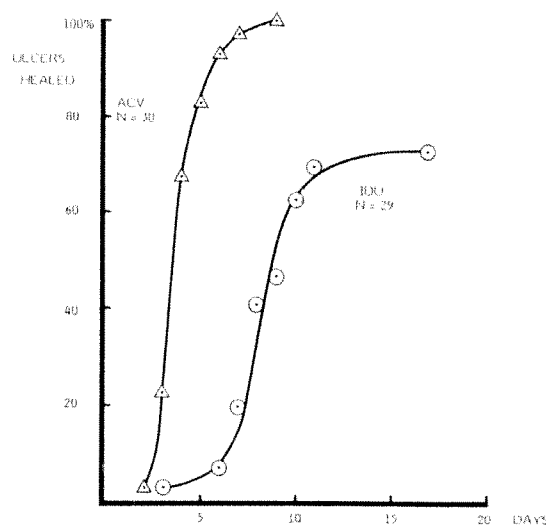


Fig. 1 Cumulative frequency distribution of time to heal dendritic corneal ulcers. ACV = acyclovir, IDU = idoxuridine.

For each symptom, resolution was more rapid after treatment with acyclovir (Table 4).

Stinging on initial application of the ointment was noted by 8 patients treated with acyclovir and by 2 patients treated with IDU. One patient treated with acyclovir complained of a sore tongue. Watering of the eye was experienced by a further 2 patients treated with IDU. This necessitated dilatation of the puncta and syringing of the duct in 1 patient. Superficial punctate epitheliopathy was noted in 6 other patients treated with IDU. Summaries of side effects for both treatment groups are given in Tables 2 and 3.

Patients in both groups have been followed up for 2.5–13 months (average 8.7 months acyclovir, 8.9 months IDU). One recurrence occurred 3 weeks after treatment with acyclovir, and 2 patients had recurrences after treatment with IDU, at 8 weeks and 4 months respectively.

Table 4 *Resolution of symptoms in patients receiving acyclovir and IDU*

Symptom	Number of days to resolve	
	Acyclovir	IDU
Pain	7.0	8.0
Photophobia	8.4	11.2*
Lachrymation	8.8	11.0†
Grittiness	7.6	9.0*

*One patient failed to resolve during treatment. †Three patients failed to resolve during treatment.

Discussion

Acyclovir was found to be superior to IDU in the treatment of superficial dendritic ulceration of the cornea, healing a larger proportion of ulcers at a more rapid rate. The proportion of IDU treated ulcers which failed to respond to treatment is similar to the average reported in previous trials. Significant side effects were not observed with acyclovir, but some patients complained of transient stinging on instillation of the ointment. No epitheliopathy was observed even in 3 patients in whom treatment was given for 20 days. Residual corneal scarring seemed to be less in the patients treated with acyclovir. This may be related to the shorter healing time in comparison with those treated with IDU.

Further studies of acyclovir are needed in patients with deeper HSV infections of the eye. Clearly the effects of topically administered acyclovir should be evaluated first. However, the drug has been administered intravenously in immunosuppressed patients with severe local and disseminated HSV infections with apparent benefit and without significant side effects,^{18,19} and combined topical and systemic administration may be an approach for the future.

We thank our colleagues who kindly allowed access to their patients, Dr W. D. Brigden and Mr T. Ravenscroft, Wellcome Research Laboratories, Beckenham, for coded supplies of acyclovir and IDU, and Mr P. Smith for the statistical analyses.

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Endogenous dissemination of genital *Herpesvirus hominis* type 2 to the eye

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SUMMARY A 33-year-old man developed *Herpesvirus hominis* type 2 (HVH-2) eye disease following a herpetic lesion of the penis. The sequence of ocular involvement suggested that the virus had been transmitted endogenously from the genital lesion: granulomatous iritis was followed by interstitial keratitis and then by dendritic keratitis. Recurrent bacterial ulcers ultimately required a conjunctival flap. The course of this man's ocular disease as well as those of other reported cases of HVH-2 adult eye infections appeared to be more severe and prolonged than that of the average patient with ocular herpes type 1 infection.

Although most herpetic ocular infections in adults are caused by *Herpesvirus hominis* type 1 (HVH-1), and the majority of genital disease is secondary to HVH-2, exceptions to these rules occur.¹⁻³ Fourteen previous cases have been reported of ocular HVH-2 infection in adults.¹⁻⁷ We report an additional case that provides strong evidence for endogenous transmission of genital HVH-2 to the eye.

Case report

On 11 March 1977 a 33-year-old white man developed a blister on the shaft of his penis 1 week after sexual activity with a new partner. A urologist who examined him 4 days later diagnosed genital herpes simplex. The genital lesion healed during the next few days, but on 22 March 1977 the patient consulted a general physician for redness and discomfort in his left eye. He was treated with corticosteroid eye drops and was referred to an ophthalmologist 2 days later. The right eye was normal by slit-lamp examination. The left eye showed a dense cellular anterior chamber reaction. The cornea had numerous and large keratic precipitates, but there was no evidence of epithelial or stromal involvement. The intraocular pressure was 60 mmHg. The patient was started on a regimen of topical corticosteroids, cycloplegics, and acetazolamide. Three days later, on 29 March 1977, his

intraocular pressure had decreased to 18 mmHg, but the anterior chamber reaction persisted. The patient received a subconjunctival corticosteroid injection, which produced some improvement. When next seen, on 9 April 1977, he was given a second subconjunctival injection of corticosteroids for an exacerbation of the anterior chamber inflammation. On 12 April 1977 interstitial keratitis and stromal infiltration were first noted in the superonasal quadrant of the cornea, but no epithelial disease was seen.

On 20 April 1977 visual acuity was 6/24 (20/80). The interstitial keratitis and a mild anterior chamber reaction persisted despite cycloplegia, topical corticosteroids, and idoxuridine (IDU). A week later bullous keratopathy and epithelial stippling were noted. Vidarabine (Vira-A) was substituted for IDU. On 6 May 1977 a flare-up of the iritis necessitated additional subconjunctival corticosteroids. The inflammation of the anterior chamber quieted somewhat, but the area of interstitial keratitis seemed to be enlarging. It was at this time that we first saw the patient.

Laboratory studies performed by the referring physician included a fluorescent treponemal antibody absorption test, erythrocyte sedimentation rate, and herpes titres at 3 and 7 weeks after the onset of ocular symptoms. All were reported as negative. A repeat herpes simplex complement fixation titre in our laboratory was 1:64.

The patient's past medical history was remarkable only for a long history of mild psoriasis, childhood rheumatic fever, and admission to hospital for

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fever of unknown origin in his early 20s. He had had bilateral 'pink eye' 2 years earlier. The patient denied ever having had labial herpes.

Our initial examination on 16 May 1977 revealed a visual acuity of 6/6 (20/20) in the right eye and counting fingers at 2 feet (60 cm) in the left eye. The right eye was normal on external, slit-lamp, and ophthalmoscopic examinations. The left eye showed a slightly injected conjunctiva with steroid deposition inferiorly. The corneal sensitivity was normal. Slit-lamp examination showed diffuse bullous keratopathy with marked stromal thickening, haze, and a moderate number of folds in Descemet's membrane. There were no epithelial defects. The central corneal thickness was 0.88 mm. A few keratic precipitates appeared to be inactive. The anterior chamber was deep and clear. The iris was not atrophic. The lens was clear. Intraocular pressure was 23 mmHg by MacKay-Marg tonometry. Gonioscopy revealed only mild trabecular pigmentation. The diffuse keratitis was felt to be most consistent with herpetic disciform disease, and the patient was started on a trial of systemic steroids. When seen 11 days later he was no better, and the steroids were discontinued.

The patient was seen next on 14 June 1977 with a dendritic epithelial defect. Treatment with vidarabine was begun again. A culture of the ulcer yielded HVH; indirect fluorescent antibody testing showed it to be type 2. On 1 September 1977 he developed a dendritic lesion of the inferotemporal cornea. This responded to treatment with vidarabine. In November 1977 the patient had a recurrence of the penile lesion, from which HVH-2 was cultured.

On 8 February 1978 a central epithelial defect was noted. Bacterial cultures showed no growth. Visual acuity was hand motions at 2 feet (60 cm). The ulcer, treated with topical polymyxin B, bacitracin, and neomycin (Neosporin) and subconjunctival gentamicin, healed over 10 days, but on 7 March 1978 the epithelium again broke down. This time the culture yielded pneumococci. In spite of subconjunctival and topical antibiotics the lesion failed to heal, and on 17 April 1978 a conjunctival flap operation was performed. The patient did well until September 1978, when the penile lesion recurred for the third time and persisted for 2 weeks. One week later he developed aching and redness in his left eye. The conjunctival flap prevented a view of the anterior chamber; the intraocular pressure was raised by tactile estimation. We felt that the patient had a reactivation of herpetic uveitis and treated him with cycloplegia. This produced symptomatic improvement. In November 1978 the patient's intraocular pressure was 32 mmHg in the left eye, and he was given timolol.

Discussion

In 1975 Oh *et al.* reported the first 2 cases of culture-proved HVH-2 ocular infection in adults.⁵ Since that time 12 additional cases,^{1,4,6,7} not including ours, have been described. In 3 of these^{1,4} no clinical data was included. The available information concerning the clinical course of 12 patients is summarised.

Three had blepharoconjunctivitis without corneal involvement. Of the 9 with corneal disease all had epithelial disease, and 6 had stromal pathology. Four of the 12 had uveitis.

Five of the 12 patients required a total of 8 surgical procedures. Two had conjunctival flaps; one for a persistent epithelial defect and the other for a corneal perforation. Of the 6 keratoplasties done 3 were for optical reasons, 2 were for structural purposes, and 1 was not specified.

Although a referral practice may tend to select for those patients with recalcitrant disease, this group of 12 patients with ocular HVH-2 appears to have had more severe and prolonged disease than the average patient with ocular HVH-1. There is experimental evidence to support this clinical observation. The conjunctivitis, corneal ulceration, pannus, and iritis that resulted from dropping HVH-2 on intact and abraded rabbit corneas were more marked and of longer duration than the changes produced by HVH-1.^{8,9} Histological studies of these corneas showed stromal inflammatory infiltrates in type 2 infection to be deeper and more severe than in type 1 infection. Infiltration of the corneal endothelium, iris, and choroid by inflammatory cells was more frequent in eyes infected with type 2 than with type 1.¹⁰

The spread of HVH-2 to different parts of the body may be via several routes: neural, haematogenous, and extrinsic. In our case, if the virus had been spread extrinsically from the penile lesion to the eye, one would have expected, as in other instances,⁶ blepharoconjunctivitis or keratitis to have been the first manifestation of the ocular infection. The fact that our patient's eye difficulties began with uveitis and that the corneal epithelial defect did not develop until several months later makes direct genito-ocular or genito-digital-ocular transmission unlikely, unless the initial corneal epithelial infection was subclinical.

Because of the distance between the penile lesion and the eye, neuronal spread is unlikely, though one cannot rule out neural transmission from the uvea to the cornea. Thus, haematogenous dissemination of the virus from the genital tract to the eye seems the most likely mode of transmission in our patient, though according to Nahmias and Roizman

HVH-2 viraemia is an infrequent finding in a healthy adult.¹¹ Eiferman *et al.*¹² in a report of 2 cases of herpetic type 1 whitlow followed by dendritic keratitis, raised the possibility of haematogenous spread of virus from the fingers to the eye. They cited the work of Sery and Forster,¹³ who found that intravenous injection of HVH-1 in rabbits could cause dendritic keratitis about 10 days later. HVH-1 has been isolated from the blood buffy coat of 4 adults with vesicular stomatitis.¹⁴ HVH-2 has been detected in the blood of 2 adult patients with meningitis.¹⁵ Becker *et al.* studied the stages of haematogenous spread of HVH in children, though they do not specify whether the virus was type 1 or type 2.¹⁶ Blood-borne dissemination of HVH-2 may occur in newborn babies,¹⁷ and a case has been reported of fatal dissemination of HVH-2 infection in an apparently healthy 20-year-old woman who had necropsy evidence of thymic dysplasia.¹⁸ Our case suggests that haematogenous spread of HVH-2 may occur in healthy adults as well.

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Glaucoma in a case of Hurler disease

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SUMMARY The electron microscopic appearances of the corneoscleral and iris tissue removed at operation from a child with Hurler disease and glaucoma showed distinctive swollen cells with intracellular inclusions similar to those which are observed in other tissues in these patients and which are due to abnormal lysosomal storage of mucopolysaccharides. Some recent observations on the possible relationship between mucopolysaccharides and the drainage of fluid from the anterior chamber are briefly reviewed and correlated with the present observations. The development of glaucoma in this patient is thought to be associated with the presence of the mucopolysaccharide-containing cells in the region of the aqueous drainage channels.

The mucopolysaccharidoses are a subgroup of the lysosomal storage diseases as defined by Hers¹ in which the inherited deficiency of a specific exoglycosidase prevents the normal lysosomal degradation of the glycosaminoglycans (mucopolysaccharides), which therefore accumulate in lysosomes and produce characteristic morphological changes. The urine also contains excessive amounts of glycosaminoglycans. Table 1 lists the mucopolysaccharidoses with their specific enzyme deficiencies, excreted glycosaminoglycans, pattern of inheritance, and the tissue systems which are mainly affected in the individual disorders. Leroy and Neetens² mention a clinical association between these diseases and glaucoma, though the glaucoma may be obscured by corneal clouding. The corneal clouding is well recognised in Hurler and Scheie diseases, the Hurler/Scheie intermediate phenotype, as well as in Morquio and Maroteaux-Lamy diseases. The youngest patients with Hurler disease whom we have encountered have been between 6 and 9 months old, and they have all had corneal clouding at this stage of the disease, when the other clinical signs are slight and the evidence for developmental delay may be quite slender. The corneae characteristically remain clear in Hunter disease, though an enzymologically proved case with this complication was recently reported.³

This paper reports the development of open-angle

glaucoma in a child with Hurler disease and describes the electron microscopic appearances in tissue from the corneoscleral junction and iris.

Materials and methods

CASE REPORT

The patient was a 6-year-old girl with all the classical clinical features of Hurler disease. Her facial features are shown in Fig. 1. She excreted excessive amounts of dermatan and heparan sulphates in her urine. The diagnosis was established biochemically by the absence of α -L-iduronidase activity from her white blood cells and cultured skin fibroblasts. Differentiation from Hunter disease was also confirmed by showing the excessive uptake and retention of ³⁵SO₄ by her fibroblasts in vitro, which was corrected by subculturing the cells in tissue culture medium in which a Hunter disease patient's fibroblasts had previously grown.⁴

She was receiving regular ophthalmic examinations at 6-monthly intervals as an outpatient when it was suspected that the ocular tensions were raised. Ophthalmic examinations showed moderate bilateral corneal clouding, corneal diameters of 11.5 mm (horizontally) and 11.5 mm (vertically) in both eyes, clear crystalline lenses, and normal fundi, but early glaucomatous cupping and pallor of the discs. Shortly afterwards, while awaiting ophthalmic examination under anaesthetic, she developed an acute left orbital cellulitis, which was associated with rapid loss of vision down to perception of hand movements only. The orbital cellulitis subsided

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Table 1 The mucopolysaccharidoses

McKusick's classification*	Eponymous name	Enzyme deficiency	Excreted glycosaminoglycans	Inheritance	Organs mainly affected
IH†	Hurler	α -L-Iduronidase	Dermatan sulphate Heparan sulphate	Autosomal recessive	Central nervous system Skeleton Viscera
IS	Scheie	α -L-Iduronidase	Dermatan sulphate Heparan sulphate	Autosomal recessive	Skeleton (mild relative to Hurler) Viscera (mild relative to Hurler)
IH/S	Hurler/Scheie	α -L-Iduronidase	Dermatan sulphate Heparan sulphate	Autosomal recessive	Phenotype intermediate between Hurler and Scheie diseases
II†	Hunter	Iduronate sulphate sulphatase	Dermatan sulphate Heparan sulphate	Sex-linked recessive	Central nervous system Skeleton Viscera Mild and severe phenotypes reported
IIIA	Sanfilippo A	Heparan N-sulphatase	Heparan sulphate	Autosomal recessive	Central nervous system
IIIB	Sanfilippo B	N-acetyl- α -D-glucosaminidase	Heparan sulphate	Autosomal recessive	Central nervous system
IV	Morquio	Hexosamine 6-sulphatase	Keratan sulphate	Autosomal recessive	Skeleton
V‡	—	—	—	—	—
VI	Maroteaux-Lamy	N-acetylgalactosamine 4-sulphatase (aryl sulphatase B)	Dermatan sulphate	Autosomal recessive	Skeleton Mild and severe phenotypes reported
VII	β -Glucuronidase deficiency	β -Glucuronidase	Dermatan sulphate Heparan sulphate	Autosomal recessive	Central nervous system Skeleton Viscera

*McKusick *et al.*¹⁸ originally proposed a numerical classification of types I–V, and this was subsequently extended.

†Both formerly called gargoylism because of the characteristic and similar facies, which is also seen in the mucopolipidoses (a group of 3 biochemically different inherited metabolic diseases) and in some cases of α -fucosidosis and mannosidosis.¹⁹

‡Originally Scheie disease, which was reclassified as mucopolysaccharidosis IS when the enzyme defect was shown to be the same as that in Hurler disease. The possibility that Hurler and Scheie diseases are due to allelic mutations and that the intermediate Hurler/Scheie phenotype (mucopolysaccharidosis IH/S) is due to double heterozygosity for the allelic mutations concerned has been widely proposed. The Hurler/Scheie phenotype could also be due to homozygosity for a third allelic mutation at the same gene locus.

promptly with antibiotic treatment but without recovery of vision. Subsequent examination under anaesthetic showed ocular tensions of: right eye 42 mmHg and left eye 38 mmHg. A clear view of the angles of the anterior chamber was not obtained because of the corneal clouding, except to note that the angles were open without any grossly abnormal features.

In view of the presence of the glaucoma, which had developed rapidly, right and left glaucoma filtering (trabeculectomy) operations were performed. The portions of tissue from the corneoscleral junction and iris removed at operation form the basis of this electron microscopic study. There was little recovery of vision after the operation.

ELECTRON MICROSCOPIC METHODS

The operation specimens were prepared for electron microscopy by fixation in 3% glutaraldehyde diluted in 0.1 M cacodylate buffer with 5% sucrose (pH 7.4) for 2 hours at room temperature followed by 1% osmium tetroxide in 0.1 M cacodylate buffer with 5% sucrose at 4°C. They were dehydrated in acetone and embedded in Spurr embedding medium.⁵



Fig. 1 The patient.

Sections 1 μm thick were prepared, stained with toluidine blue, and examined. Ultrathin sections were then cut with a diamond knife on a Sorvall Porter-Blum II microtome, mounted on copper grids, and stained with saturated uranyl acetate in 50% alcohol for 10 minutes and with lead citrate for 3 minutes. They were stabilised with a light coat of carbon and examined in a Phillips EM 300 electron microscope. Some control iris tissue from a case of open-angle glaucoma, which was not associated with Hurler disease, was similarly processed for electron microscopic examination.

Results

CORNEOSCLERAL JUNCTION

The tissue from the corneoscleral junction consisted of dense bundles of collagen fibres with cells (presumed to be fibroblasts) lying between the bundles. The 1 μm toluidine blue sections showed these cells to have considerably swollen and foamy cytoplasm (Fig. 2). The ultrathin sections from these areas showed that the cytoplasm of nearly every cell contained numerous membrane-bound vesicles which either appeared completely clear or contained faint floccular staining and occasional membranes (Fig. 3).

IRIS

Similar membrane-bound inclusions were found in the cells in the sections from the iris. The highly pigmented cells with numerous melanosomes in

general did not show these inclusions, but they were very prominent in the underlying stromal cells (Fig. 4). Similar inclusions were not seen in the corresponding cells in the control iris tissue (Fig. 5).

CONJUNCTIVA AND TENON'S CAPSULE

Similar cellular inclusions were found in the cells lying between the collagen bundles in this tissue.

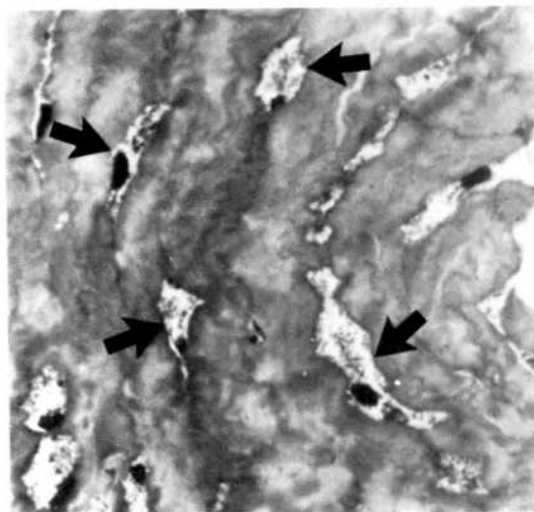


Fig. 2 1 μm thick section of tissue from the area of the canal of Schlemm. Cells with greatly swollen cytoplasm lying between bundles of collagen fibres (arrows). (Toluidine blue $\times 640$).

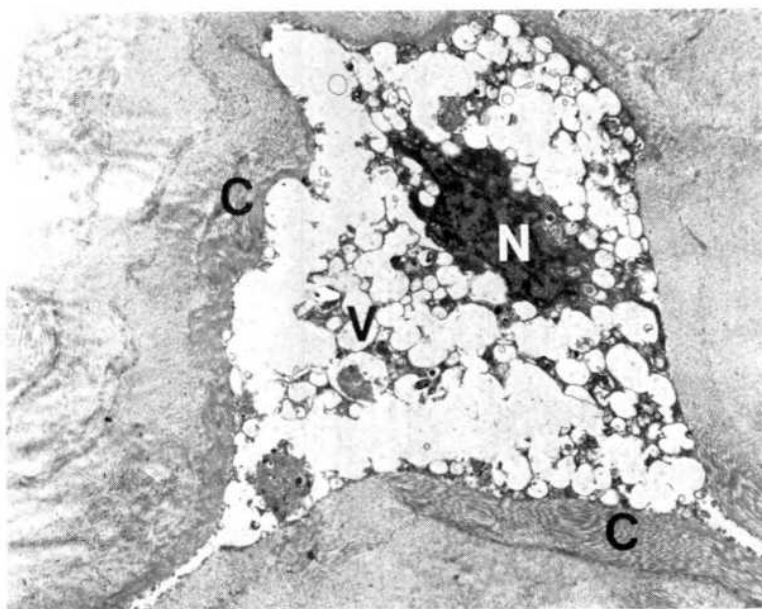
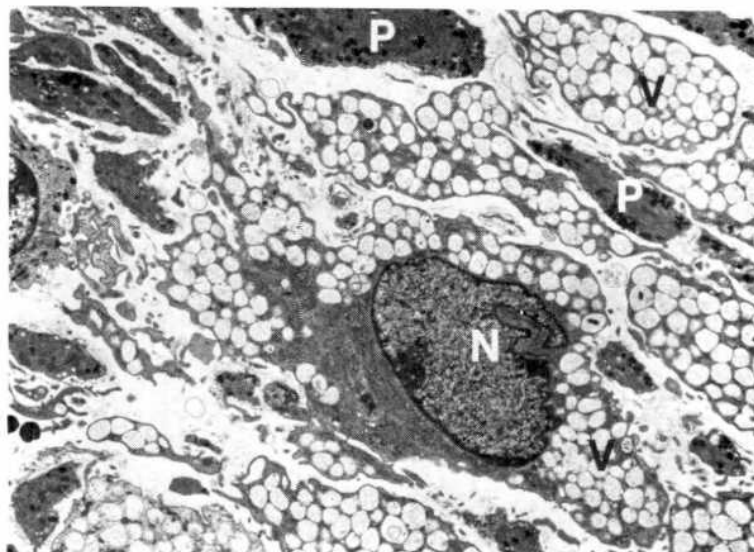


Fig. 3 Electron micrograph of tissue from the area of the canal of Schlemm. The cell cytoplasm is greatly distended by membrane-bound vesicles some of which have coalesced and contain faintly staining material and occasional membranes. N = nucleus, V = vesicles, C = collagen. ($\times 3840$).

Fig. 4 Electron micrograph of tissue from the iris. The cytoplasm of many of the cells contains numerous membrane-bound vesicles with faintly-staining contents. N = nucleus. V = vesicles. P = cells with pigment granules. ($\times 3560$).



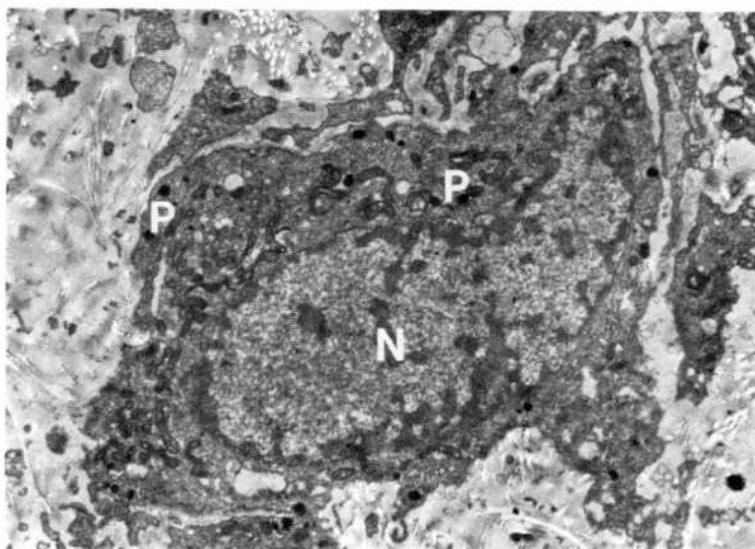
Discussion

Corneal clouding, retinal pigmentary degeneration, and optic atrophy may all arise as complications of Hurler disease,⁶ and corneal clouding is a consistent, very early sign of the disease. The optic atrophy is of multifactorial origin and may be associated with the retinal pigmentary degeneration, damage to the ganglion cells, mucopolysaccharide deposition within the optic nerve, papilloedema due to hydrocephalus, and glaucoma. The present patient remained blind after the technically success-

ful trabeculectomy operations, which indicated direct damage to the visual pathway by either abnormal mucopolysaccharide deposits or complicating vascular occlusion. She was subsequently shown to have progressive internal hydrocephalus with raised intraventricular pressures.

The electron microscopic appearances of the cells in the corneoscleral junction, the iris, and conjunctiva from this patient are similar to those described in other tissues in the disease⁷ and observed by us in the sebaceous glands of skin biopsy from this patient (Fig. 6). Quigley *et al.*⁸ reported 2 sibs

Fig. 5 Electron micrograph of control iris. Cell containing a few small pigment granules but no large membrane-bound vesicles. N = nucleus. P = pigment granules. ($\times 8290$).



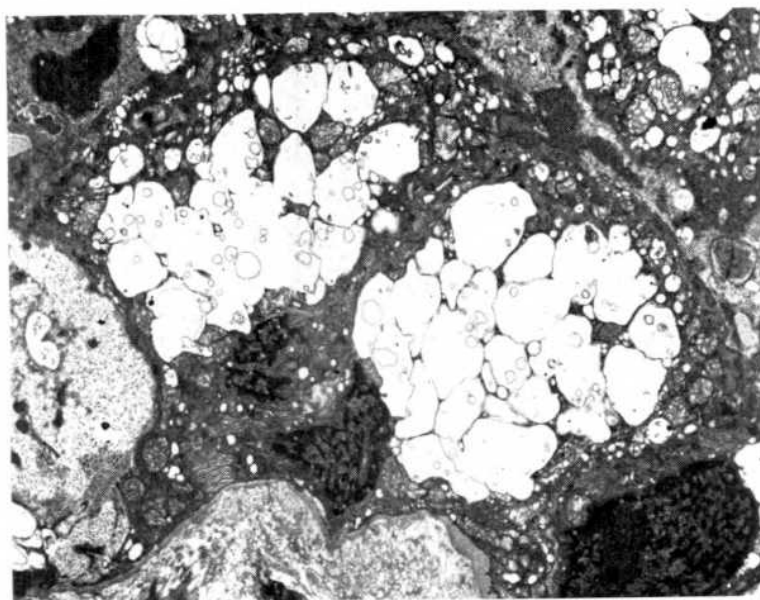


Fig. 6 Electron micrograph of cells in the patient's dermis showing similar membrane-bound inclusions to those seen in the eye. ($\times 4945$).

with biochemically proved Scheie disease (mucopolysaccharidosis IS) who developed acute glaucoma. Like ourselves, these workers could not identify any trabecular meshwork in the tissue which was removed surgically, though Descemet's membrane was seen in one specimen. Histochemical staining (colloidal iron and Alcian blue) showed extracellular acidic mucopolysaccharide deposits which were resistant to hyaluronidase.

D'Epinay and Remé⁹ described a patient with glaucoma and clinical features resembling either one of the gargoyl-like mucopolysaccharidoses (types IH, II, VII; Table 1), one of the mucopolysaccharidoses (types I, II, and III¹⁰), or some cases of mannosidosis and fucosidosis.¹⁰ These workers⁹ examined tissue from their patient by electron microscopy and reported intracellular storage vacuoles in the cells lining the drainage canal as well as extracellularly. They also described rupture of the endothelial lining of the canal. Unfortunately their case report lacks any diagnostic biochemical data. Glaucoma is known to occur in Scheie disease, mucopolysaccharidosis IS¹¹ (Table 1), and in the Hurler/Scheie intermediate phenotype.¹² The lack of reported cases in proved Hurler disease may be related to the short life span, with death occurring before the development of glaucoma; or the masking of glaucoma by severe corneal clouding; or the lack of detailed ophthalmological examination in a child severely retarded by a disease known to produce blindness of multifactorial origin.

There is increasing awareness of the clinical and therefore possible genetic heterogeneity within the

individual mucopolysaccharidoses as well as the clinical similarities between the diseases themselves. Therefore earlier reports relating to the different diseases require critical evaluation, because the enzymological techniques necessary to identify them definitively were rarely available.

Evidence suggesting the possibility of a specific association between the mucopolysaccharidoses and the development of glaucoma arises from an observation of Peterson and Jocson,¹³ whose perfusion studies with enucleated rhesus monkey eyes showed that hyaluronidase reduces the aqueous outflow resistance. They concluded that the presence of mucopolysaccharides in the outflow apparatus is a factor influencing the normal drainage of fluid from the anterior chamber. Confirmatory studies in man have been possible only on eyes containing orbital tumours.¹⁴

Hyaluronidase breaks down glycosaminoglycans by splitting the internal glycosidic bonds between the individual sugar residues and not by sequential degradation of the polysaccharide chain, as is the case with exoglycosidases, specific deficiencies of which cause the mucopolysaccharidoses—for example, α -iduronidase deficiency and Hurler disease. This effect of hyaluronidase on ocular drainage could be by virtue of its action on either extracellular or intracellular deposits of the glycosaminoglycans, since the enzyme could gain access to the interior of the cells by pinocytosis. The mucopolysaccharides are incompletely degraded in Hurler disease and accumulate in the extracellular fluid¹⁵ as well as in lysosomes and may in turn inhibit other degradative

enzymes including hyaluronidase,¹⁶ and this could result in an increased resistance to aqueous outflow.

The drainage of fluid from the anterior chamber of the eye is also thought to depend on the formation of temporary vacuoles in, or vacuolar channels across, the endothelial lining of the outflow apparatus.^{14,17} If the cytoplasm of these endothelial cells is disrupted by stored mucopolysaccharide in the same way as the connective tissue cells which we have demonstrated, it is likely that this function will be impaired. This is another possible mechanism by which the abnormally stored mucopolysaccharides could interfere with aqueous drainage and cause glaucoma.

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Addition of timolol maleate to routine medical therapy: a clinical trial

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SUMMARY A double-blind cross-over trial of timolol maleate (Timoptol) while routine medical therapy was continued gave the result that pressure was reduced by 3.22 mmHg as compared to placebo and 5.01 compared to pre-timolol levels in 24 patients. There was also a small (1.858 mmHg) drop in pressure in placebo treated eyes, a small and statistically significant drop in resting pulse rate, 76.67 to 71.39/min, and a small but not statistically significant drop in diastolic blood pressure.

Timolol maleate, a beta adrenergic blocking agent, has been shown to be effective in reducing intraocular pressure in patients with open-angle glaucoma.¹⁻⁴ A trial was undertaken to measure the degree of further pressure reduction which timolol maleate (Timoptol) would produce in patients already taking medical therapy. The question of whether any improvement found would afterwards be maintained will be the subject of a further study.

Material and methods

Twenty-four patients with chronic open-angle glaucoma were selected. They were already on topical medication but not on acetazolamide and had not had previous surgery except for one, No. 18, who had had a right trabeculostomy followed by trabeculectomy 1 year previously. They were on a variety of other medical treatments, the commonest pattern being pilocarpine 4% 4 times daily plus guanethidine 1% and adrenaline 0.5% twice daily. Other regimens in use were pilocarpine 4% 4 times daily plus guanethidine 1% and adrenaline 0.25% twice daily, and in a few cases pilocarpine alone or guanethidine and adrenaline alone.

The age range of the patients was 22 to 81 years with an average of 63. Nine were men and 15 were women. Those admitted to the trial had a regular pulse rate of 61 or more and a blood pressure of 120/70 mmHg or more. The patients were informed of the nature of the trial and consent was obtained.

Each patient was seen at an initial session and the following data were recorded: name, age, sex, date and time of day, intraocular pressure in each eye,

visual acuity, blood pressure, and pulse rate (resting).

Existing therapy was continued and the hospital pharmacy also issued 2 extra bottles (one containing the drug and the other normal saline), instructing the patient to instil 1 drop in 1 eye from 1 bottle and another in the other eye from the other bottle 10 minutes after the already prescribed drops each morning and evening for 1 week.

The patients were examined at weekly intervals. At the conclusion of the third week the therapy was altered so that drug and saline were now instilled in the opposite eyes and the examinations continued for a further 3 weeks. When all had completed their 6-week course the results were reviewed.

The code as to which eye was receiving timolol and which placebo was held in the pharmacy. Unfortunately patients were probably aware which was timolol and which was placebo, since the timolol was issued in a distinctive bottle. Thus only the observers were unaware of the distribution of drug and placebo during the trial.

Results

The code by which drug or placebo was issued ensured that in 12 of the 24 patients Timolol would be added first in the right eye whereas in the other 12 it would be added first in the left. The possible combinations were therefore as follows:

Right eyes. Timolol first 3 weeks; placebo second 3 weeks, designated RT1-RP2 (12 eyes of patients 2, 3, 6, 8, 9, 12, 15, 16, 19, 20, 23, and 24). Timolol second 3 weeks; placebo first 3 weeks, designated RT2-RP1 (remaining 12 patients).

Left eyes. Timolol second 3 weeks; placebo first 3 weeks, designated LT2-LP1 (same 12 patients as

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group RT1-RP2 above). Timolol first 3 weeks; placebo second 3 weeks, designated LT1-LP2 (same 12 patients as group RT2-RP1 above).

In each of these categories RT1-RP2 etc. 3 intraocular pressures have been recorded on 12 patients, that is, 36 pressures. In the analysis of results, therefore, the figure given for each category is the mean of these 36 readings. In addition the pressure found at the initial examination has been recorded and is expressed as the pretreatment pressure. The mean for each group of 12 eyes is listed; for example, in the group RT1-RP2 the pretreatment figure RT1 (pretreatment) is the mean of all pretreatment pressures for those 12 eyes.

Comparisons can now be made as follows: timolol treated pressures can be compared with pretreatment pressures, for example, RT1-RT1 (pretreatment), or with placebo pressures in the same eyes, for example, RT1-RP2. Results are shown in Table 1.

It will be seen from the table that in each group timolol pressures were lower than placebo pressures by an amount which was statistically significant except in the group LT1. The differences from pretreatment at -3.89 mmHg or from placebo at -4.36 mmHg, though large, fail to achieve significance because of 1 patient who showed bizarre readings in the left eye, where pressures varied between 24 and 64 during the trial period.

The pooled results expressed as All T-All P show a difference of -3.22 mmHg. In other words, the addition of timolol appeared to be associated with a lowering of pressure of 3.22 mmHg in the 48 eyes of 24 patients. Timolol pressures are also lower than the pretreatment pressures by an amount greater than the T-P result, namely -5.01.

The comparison of placebo pressures with pretreatment pressures can also be made, and in 2 cases (LP1-LP1 (pretreatment) and RP2-RP2 (pretreatment)) the differences exceed -3.00 and are statistically significant. If the total mean drop in placebo eyes compared to pretreatment eyes is examined it comes to -1.858, and this difference is statistically significant at the 5% level.

The effect of timolol in this study does not appear to be related to the initial intraocular pressure, since there is no correlation between the mean pressure drop in the 2 eyes in each patient and the pre-timolol pressure. Similarly, there seems to be no correlation between the pressure drop obtained in each patient and the type of treatment being used initially: for example, pilocarpine 4%, guanethidine 1% and adrenaline 0.5%, or pilocarpine alone or guanethidine and adrenaline alone.

The mean diastolic blood pressure of the patients before timolol was 92.25 mmHg and the mean of

Table 1 Intraocular pressure

	Average pressures (mmHg)	Difference	Significance (Student's t) P <
<i>Right eyes</i>			
RT1-RT1 (pretreatment)	19.97-25.75	-5.78	0.001
RT1-RP2	19.97-22.55	-2.58	0.01
RT2-RT2 (pretreatment)	20.69-25.00	-4.31	0.1
RT2-RP1	20.69-24.37	-3.64	0.01
RP1-RP1 (pretreatment)	24.33-25.00	-0.67	0.7
RP2-RP2 (pretreatment)	22.55-25.75	-3.20	0.02
<i>Left eyes</i>			
LT1-LT1 (pretreatment)	19.86-23.75	-3.89	0.1
LT1-LP2	19.86-24.22	-4.36	0.1
LT2-LT2 (pretreatment)	18.10-24.41	-6.31	0.001
LT2-LP1	18.10-20.69	-2.59	0.05
LP1-LP1 (pretreatment)	20.69-24.41	-3.72	0.01
LP2-LP2 (pretreatment)	24.22-23.75	+0.47	0.9
ALL T-ALL P	19.65-22.87	-3.22	0.001
ALL T-ALL T (pretreatment)	19.67-24.68	-5.01	0.001
ALL P-ALL P (pretreatment)	22.87-24.73	-1.86	0.05

Table 2 Diastolic blood pressure

<i>Pre-timolol</i>		<i>On timolol</i>	
n	=24	n	=144
Mean	=92.25 mmHg	Mean	=89.26 mmHg
SD	=7.70	SD	=9.82
Difference = 2.99			
t = 1.69			
n = 168			
0.1 > P > 0.05 (not significant)			

Table 3 Resting pulse rate

<i>Pre-timolol</i>		<i>On timolol</i>	
n	=24	n	=144
Mean	=76.67	Mean	=71.39
SD	=8.62	SD	=8.77
Difference = 5.28			
t = 2.77			
n = 168			
P < 0.01 (significant)			

the 144 readings (6 readings on each of the 24 patients) while on timolol was 89.26. The difference failed to achieve significance (Table 2).

The mean resting pulse rate dropped from 76.67/min before timolol to 71.39 during treatment. The difference was statistically significant (P < 0.01).

Discussion

The table of pressure readings in eyes receiving timolol maleate (Timoptol) or placebo first or second and the pressure readings in the same eyes before treatment, as previously described, enable the conclusion to be drawn that the addition of timolol to existing treatment appears to be associated with a drop in pressure during the 3-week period of approximately 3 mmHg. This is in close accord with the findings of Keates,⁵ who has carried out a very similar study. His difference was expressed in percentage terms as 15%; our result expressed in the same terms would be approximately 15%.

As described above, this pressure drop varies somewhat. For example, it is as high as 6.31 mmHg in left eyes on timolol for the second 3-week period compared to their pretreatment pressure and as low as 2.58 mmHg in right eyes on timolol first as compared with the same eyes on placebo 3 weeks later.

The average for all the timolol versus placebo eyes is -3.22 in favour of timolol, and the average for all timolol pressures versus all pretreatment pressures is -5.01 in favour of timolol.

This is a short-term study which was designed to give a preliminary idea in as short a time as possible of what could be expected from this new drug when added to existing treatment. The trial tells us nothing of the relative merits of timolol maleate versus any other form of treatment nor does it tell us whether the timolol effect is likely to be maintained in the long-term.

It is interesting that a small but statistically significant drop in pressure occurred in the placebo eyes. It is not possible to say whether this is due to observational error, patient error (since the patients were unfortunately able to identify the drug), or to a genuine pharmacological effect, possibly of a systemic nature.

Side effects of the drug were not striking. One patient complained of misty vision in one eye at one visit, but when the code was broken this proved to be the eye taking placebo. Another patient gave up timolol soon after completion of the trial for symptoms of discomfort and headache, and 1 patient complained of mild stinging from the timolol. There were no other definite complaints.

Pulse rates were significantly slowed from a mean of 76.67 to 71.39/min, and diastolic blood pressure was lowered from 92.25 to 89.26 mmHg, a drop of 3 mmHg, which was not statistically significant.

One rather disconcerting event has to be recorded. The first patient in the trial, a 72-year-old male, died suddenly in the third week of the trial. None of his results are used in the statistics and his place was filled by another patient. The cause of death was given as myocardial ischaemia and fibrosis due to atheroma. The patient's blood pressure was recorded as 170/100, 160/98, and 162/100 mmHg and his pulse rate as 72, 74, and 72/min at the preliminary examination and at the first and second weekly visits of the trial.

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Ophthalmic manifestations of primary oxalosis

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SUMMARY The clinical and pathological findings of a 6-month-old infant with primary oxalosis, who died in renal failure, are presented. The oxalate crystalline deposition in the retinal pigment epithelium corresponded to the flecked retinopathy observed ophthalmoscopically. The difficulties in establishing a precise biochemical diagnosis are discussed and the relevant ophthalmic literature is reviewed.

Oxalate is an end product of metabolism which can be removed from the body only by the kidney. Therefore, if the total body oxalate increases, whether from increased ingestion of oxalate (or a precursor), hyperabsorption, or increased synthesis of this substance, hyperoxaluria will result, and in certain circumstances insoluble calcium oxalate in the tissues will be deposited to create the condition known as oxalosis. Although oxalate crystals have been recognised in urine for over a century, it was not until the 1950s that the metabolic and hereditary significance of hyperoxaluria was appreciated, and at present 2 variants of primary hyperoxaluria are recognised, both of which are uncommon and inherited in an autosomal recessive mode.

Type I hyperoxaluria is due to a deficiency of the cytoplasmic enzyme α -ketoglutarate: glyoxylate carboligase.¹ Normally, under the influence of this enzyme glyoxylic acid, derived in the first instance from the breakdown of glycine, combines with α -ketoglutarate to form α -hydroxy- β -keto adipate. In its absence, however, glyoxylic acid is diverted to form glycolic acid and oxalic acids, the latter being irreversible, with the accumulation and increased urinary excretion of oxalic, glycolic, and, at times, glyoxylic acids.² Although Bourke and co-workers³ recently have described a patient with high urinary oxalate and glycolate levels, but normal α -ketoglutarate: glyoxylate carboligase activity, these workers used skeletal muscle, whereas Koch *et al.*'s¹ study related to the activity of this enzyme in liver, kidney, and splenic homogenates (Fig. 1).

Type II hyperoxaluria is characterised by a urinary excess of both oxalic and L-glyceric acids.

Leucocyte D-glyceric dehydrogenase has been found to be deficient in 4 patients with this disorder, leading through the action of lactic dehydrogenase to increased production and urinary excretion of L-glycerate from the reduction of hydroxypyruvate.⁴ The increase in oxalate synthesis is considered to reflect a concomitant oxidation of glyoxylate in response to lactic dehydrogenase activity.

Most patients with primary hyperoxaluria present in the first few years of life. Renal tract involvement dominates the clinical picture, with nephrolithiasis usually progressing to renal failure and death from uraemia within 10 years. It is, however, unusual for this condition to become apparent within the first year of life, only 16 of 105 recorded cases reviewed by Hockaday *et al.* presenting at this early age, and many of these presenting atypically.⁵ The patients with type II hyperoxaluria so far reported have run a relatively benign course, remaining alive and well for over 15 years.²

Secondary hyperoxaluria may occur in many conditions, including ingestion of oxalic acid⁶ or a precursor such as ethylene glycol,^{7,8} hyperabsorption of oxalate following small bowel resection,⁹ renal failure,¹⁰⁻¹² sarcoidosis, and cirrhosis of the liver.¹³ Both thiamine and pyridoxine deficiencies cause hyperoxaluria in the experimental animal, but their role in the production of this state in man has yet to be clarified.² The anaesthetic agent methoxy-flurane, which is also a precursor of oxalic acid may cause renal failure,¹⁴ hyperoxaluria,¹⁵ and even retinal oxalosis.¹⁶

Case report

A caucasian male was born on 11 July 1978 with a birth weight of 7 lb 15 oz (3600 g) after an uneventful pregnancy. There was no family history of renal

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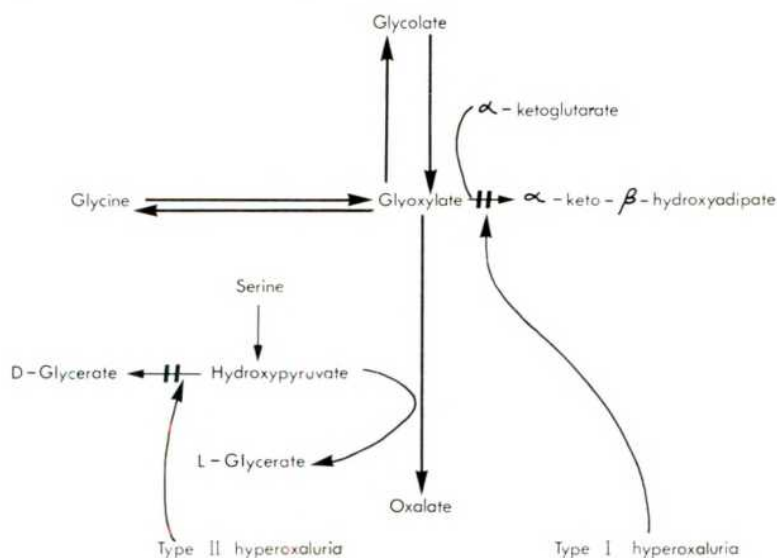


Fig. 1 Simplified diagram of oxalate metabolism.

disease, and the other sib, a boy aged 3 years, was healthy. Development was normal until the age of 5 months, when he contracted an upper respiratory tract infection. Within a few days he began vomiting after every feed and was admitted to the Derbyshire Children's Hospital 1 month later (4 January 1979) having been anuric for 48 hours. Over the ensuing 20 days peritoneal dialysis was undertaken in 3 periods for a total of approximately 150 hours.

Despite his poor general condition and age he was visually alert on examination and responded to an optokinetic stimulus. The anterior segments of the eyes appeared normal. The posterior poles of both retinæ contained numerous minute round white flecks, which did not extend either to the optic disc or beyond the main vascular arcade. These areas were situated in the deeper retinal layers and appeared as pigment epithelial defects (Fig. 2).

Pyridoxine was administered, on an empirical basis, 50 mg intravenously 6 hourly for 3 days, but unfortunately no clinical improvement was obtained, and the infant, who had by this time been essentially anuric for 3 weeks, died on 24 January 1979.

Investigations

Blood. Before dialysis: Na 125 mmol/l, K 7.13 mmol/l, Cl 89 mmol/l, Ca 1.26 mmol/l, urea 67 mmol/l, creatinine 1384 μ mol/l. During dialysis: glycolate 23 μ mol/l (normal), oxalate 33 μ mol/l (raised), L-glycerate 6.6 μ mol/l (normal values as yet undetermined but probably normal).

Urine. Persistent anuria, no analysis possible. Plain abdominal x-ray showed diffuse nephrocalcinosis.

Renal biopsy. Glomeruli essentially normal for age. Almost all proximal tubules were packed with large crystalline aggregates, and the associated epithelial cells were either unidentifiable or degenerate. Some crystals had broken through the interstitium and stimulated a fibrotic and chronic inflammatory cellular infiltrate. Under partly polarised light the crystals showed the birefringent pattern of oxalate. The findings were confirmed by electron microscopy.

Bone marrow. A specimen obtained from the

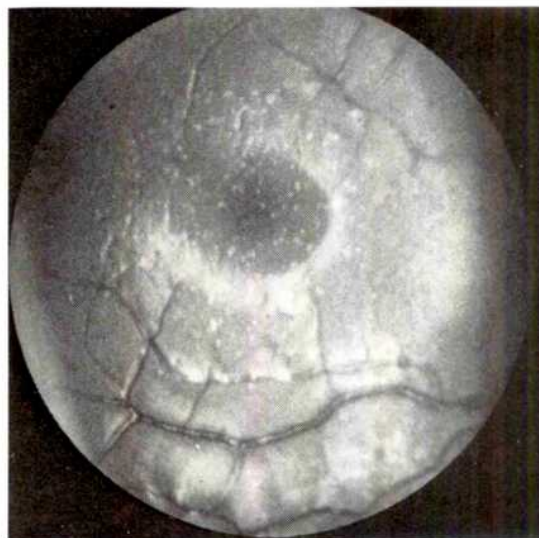


Fig. 2 White flecks in the posterior fundus of the right eye.

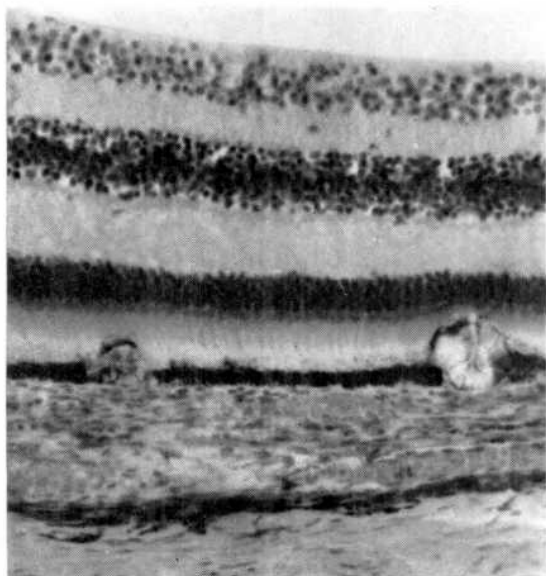


Fig. 3 Crystalline deposits of calcium oxalate in the pigment epithelium of the posterior retina. (Haematoxylin and eosin, $\times 180$).

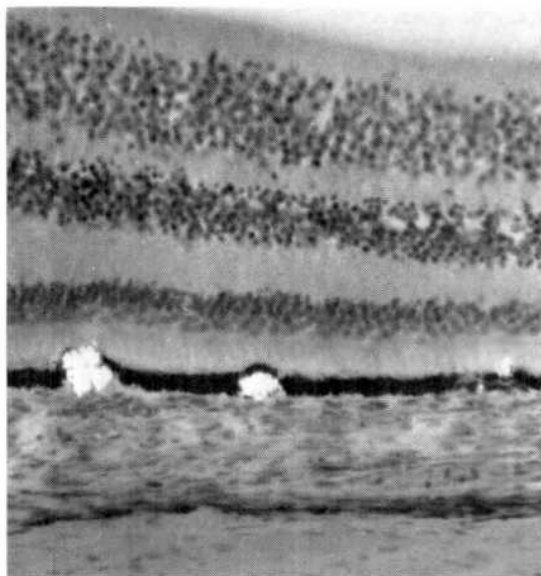


Fig. 4 Calcium oxalate crystals viewed through partially crossed polarising screens. (Haematoxylin and eosin, $\times 180$).

anterior iliac crest did not contain any crystalline deposition.

Post-mortem pathology. The kidneys were of normal size (right 40 g, left 35 g) but the tubules were found to be packed with crystals. Crystals were also found in the heart, lung, thymus, thyroid, brain stem, adrenals, pancreas, and testis.

OCULAR HISTOPATHOLOGY

The eyes were removed 5 hours after death. There was no discernible external abnormality of either globe.

The cornea, iris, ciliary body, and lens were normal and showed no evidence of crystal deposition. The posterior segment tissues were well formed and the retina was in situ. Towards the posterior pole, however, the retinal pigment epithelium showed several isolated crystalline deposits, which were colourless and birefringent (Figs. 3 and 4). The deposits consisted of sheaths of acicular crystals, and Yasue's stain for calcium oxalate was positive (Fig. 5). The smaller crystalline deposits were intracellular, whereas larger accumulations were associated with disruption and degeneration of the pigment epithelium (Fig. 6). Very occasionally crystals were seen within the neuroretina and were presumed to have migrated from their original location. Some penetration of Bruch's membrane with encroachment on the choroid was also observed in relation to the larger crystals.

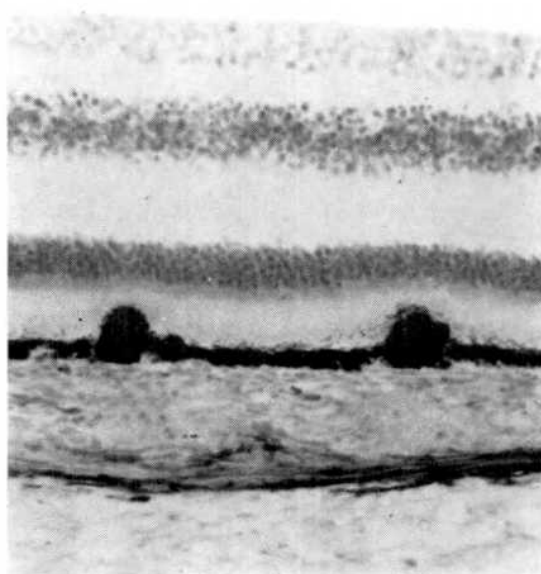


Fig. 5 The calcium oxalate crystals are stained black by Yasue's silver-rubeanic acid technique ($\times 180$).

Discussion

By definition the diagnosis of primary hyperoxaluria rests on the presence, in excess, of urinary oxalic and either glycolic or glyceric acids, and in

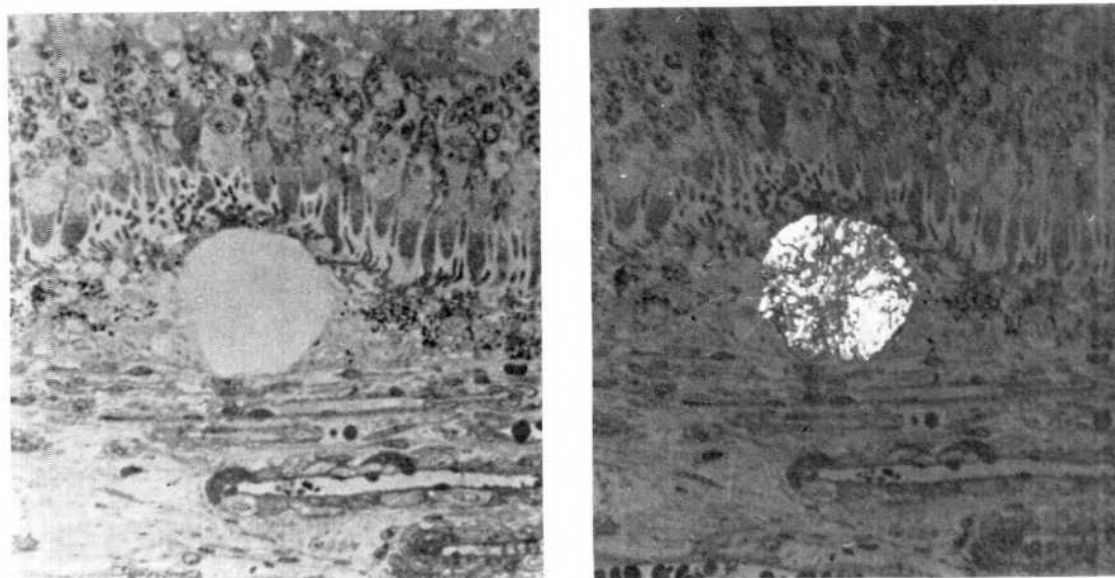


Fig. 6 Section 1 μ m thick of Araldite-embedded retina viewed (left) by conventional microscopy and (right) by polarising microscopy, showing a crystalline deposit within the retinal epithelium. (Toluidine blue, $\times 450$).

most instances such measurements can readily be made. In the present case, however, the persistent anuria precluded such estimations. The use of plasma oxalate levels has proved to be of limited value, as levels may rise in renal failure unrelated to oxalosis, though patients with primary hyperoxaluria tend to have higher concentrations than other patients with comparable blood urea¹¹ or creatinine¹² levels. Serum oxalic acid in our patient was estimated after peritoneal dialysis had started, and although the effect of this treatment on the plasma levels of this substance is not known with certainty it has been shown that peritoneal dialysis is not an efficient method of oxalate removal.¹⁷

Other diagnostic possibilities which should be considered in this case are ingestion of oxalic acid (or precursor) or oxalosis secondary to renal failure. The limited mobility of a breast-fed 5-month-old infant eliminates the first, while the lack of renal pathology except for that attributable to oxalate deposition makes oxalosis secondary to renal failure unlikely. We therefore conclude that this infant suffered a primary disturbance of oxalate metabolism. Further consideration of this aspect is beyond the scope of this article, but as Williams and Smith state, 'the diagnosis of primary hyperoxaluria in the uraemic stage of the disease may be difficult to document by current methods'.²

Oxalate crystals have been found to be deposited in many tissues of the body, including bone,^{18,19}

heart,^{18,19} thyroid,¹⁸ and testis,¹⁸ with little or no clinical significance. Heart block due to involvement of the cardiac conduction tissues has been reported,^{19,20} and presumably the pendular nystagmus noted by Gottlieb and Ritter²¹ resulted from macular involvement.

So far oxalate deposition in extrarenal tissues has been considered in conditions in which there has been a disturbance of oxalate metabolism, but its deposition in the eye can occur in the absence of a systemic disturbance. Thus oxalate crystals have been detected in the lens in association with phacolytic glaucoma²² and Morgagnian cataract²³ and in the retina or adjacent tissue fluid in long-standing retinal detachments.²³⁻²⁷

The above are all instances of calcium oxalate deposition in degenerate tissue, and in none of these cases has there been a generalised disorder of oxalate metabolism.

The first report of ocular involvement in primary hyperoxaluria was when Scowen and colleagues detected crystals in the ciliary body as an incidental post-mortem finding.¹⁸ Brini confirmed this finding in a young adult who died from primary hyperoxaluria, noting crystals in the stroma of the ciliary processes.²⁸ Franceschetti in a description of a 9-year-old girl with primary hyperoxaluria, was the first to observe retinopathy.²⁹

In 1963 Timm observed inflammation of the extraocular muscles associated with crystalline

deposits in the walls of their vascular supply in a patient with oxalosis; the ciliary body, choroid, optic nerve, and retina were also involved. The deposits in this last tissue were situated in the ganglion cell layer.³⁰ A second report by this author concerns an eye enucleated for secondary glaucoma.³¹ Crystals were seen in all layers of the retina (predominantly the inner), retinal arterial walls, optic disc, and ciliary body. Vitreous membranes and haemorrhage were observed in addition to rubeosis iridis. Later the remaining eye developed white spots in the retina followed by a proliferative retinopathy and vitreous haemorrhage. This patient was in renal failure, but unfortunately owing to the paucity of systemic and biochemical data the nature of the basic pathological process is not clear. The involvement of the inner retinal layers, retinal arteries, and the later development of proliferative retinopathy are at variance with other reports, and it is not known whether they represent a later stage or different pathological process to that observed by others.

Toussaint *et al.* reported the clinical and pathological findings of a male with primary hyperoxaluria.³⁰ White spots were seen to develop at both retinal posterior poles 1 month before death. Crystals were observed between Bruch's membrane and the retinal pigment epithelium and a few were seen to be intraepithelial. Crystals were present in the ciliary body stroma, only occasionally reaching the pigment epithelium.

In 1977 Gottlieb and Ritter observed multiple white retinal flecks in an infant with type I hyperoxaluria. Initially the maculae were spared, but by the age of 9 months pendular nystagmus and macular involvement was seen. Pathological examination was not performed.³¹

Ocular involvement in secondary hyperoxaluria has been reported by Bullock and Albert and colleagues^{14,22} in a patient who died of renal failure following abdominal surgery under methoxyfluorane anaesthesia. A flecked retinopathy, which did not affect vision, was seen, while histological examination of the eyes revealed multiple birefringent crystals in the retinal pigment epithelium involving the posterior pole and extending to the mid periphery. A few crystals were also observed in the ciliary body.

Despite the limited number of patients with either primary or secondary oxalosis in whom a retinopathy has been observed an evolutionary pattern is apparent. Initially small white flecks (appearing as minute depigmented areas in the deeper retinal layers) are seen at the posterior retinal poles, later spreading peripherally and in 1 case centrally to involve the macula. The histopathological changes

are similar in most reports, crystals being detected in either the ciliary body or retina or both. It is not possible to state unequivocally whether the crystals originate intra- or extra-cellularly, but it is our impression, and that of Bullock *et al.*,³² that they begin intracellularly and later disrupt the cell. The acicular appearance supports this theory and may also account for the observations^{18,20,28} that crystals were situated in the ciliary body stroma, for, if the illustrations³⁰ are studied, crystals are seen abutting on the pigmented ciliary epithelium and in fact may have arisen from this layer, particularly as crystals have been observed in these cells.¹⁸ Retinal pigment epithelial involvement has been noted in 3 reports^{18,20} including the present case.

So far only the clinicopathological changes which sometimes occur in hyperoxaluria have been discussed, but it is interesting to consider a few factors which may influence calcium deposition in the eye and its predilection for the pigment epithelium.

The metabolic precursors of oxalic acid in man are ascorbic acid, glyoxylate and certain aromatic amino acids (tryptophan, tyrosine, and phenylalanine). Just under half the daily urinary excretion of oxalate is derived from ascorbic acid via a pathway which is ill understood but probably does not involve glyoxylate as an intermediary.³³ Whether such a pathway exists in the eye is unknown, but this possibility should be considered, firstly because owing to active transport the concentration of ascorbic acid in human aqueous is 20 times that of plasma,³⁴ and secondly because retinal microsomes in certain vertebrates have been shown to concentrate ascorbic acid via an energy dependent process.^{35,36} The concentration of this substance in the vitreous is much lower than in the aqueous but is still higher than in the plasma.³⁷ Ascorbate levels in aqueous and vitreous were found to be decreased in naphthalene-fed rabbits, this being attributed to oxidation of ascorbate and its subsequent breakdown to oxalate.³⁸ Calcium oxalate crystals were deposited in the vitreous and on the inner surface of the retina^{39,40} but not in the deeper retinal tissues. It is difficult to imagine that intraocular oxidation of ascorbate to oxalate has a significant role in hyperoxaluria, particularly as the site of deposition (pigment epithelium of ciliary body and retina) may be considered to be 'upstream' to the regions of ascorbate transport or concentration. Furthermore, involvement would be expected either to be generalised or to occur in regions of high ascorbate concentration rather than in the characteristic localised pattern observed.

Since there is no evidence that oxalate is synthesised locally, and since most membranes are per-

meable to this substance,⁴¹ it is reasonable to suggest that it diffuses into the pigment epithelium from the submacular choroidal circulation. Why the pigment epithelium should be selectively involved is not known. As the low solubility of calcium oxalate is hardly altered between pH 5 and 8.2, intracellular pH changes cannot be significant,⁴² but whether other ions which could affect its solubility are present, or whether naturally occurring inhibitors to crystal growth such as exist in the urine are absent, is unknown.

Calcium influences many vital cellular activities including enzymatic and membrane-linked functions, so that it is important for cytoplasmic calcium to be protected from the considerable fluctuations in concentration to which extracellular calcium is subject. The Ca^{2+} content of the extracellular fluid at 10^{-3}M is at least a thousand times that of the cytosol (10^{-6} to 10^{-7}M), and, while both mitochondria and microsomes are rich in this cation, how much of this remains in its ionised state in these organelles is unknown.⁴³ In order to maintain a constant cytosol Ca^{2+} level mechanisms exist to control its movement in and out of the cell and into the mitochondria and microsomes. The homeostatic mechanism is liable to be overwhelmed, however, by the influx of large amounts of oxalate which complex with the ionic intracellular calcium and precipitate to form poorly soluble crystals.

The acicular pattern of crystal formation observed indicates intracellular origin, and we therefore suggest that in the first instance oxalic acid diffuses into the retinal pigment epithelium, where for reasons as yet unknown precipitation as its insoluble calcium salt occurs. Once initiated, crystallisation continues apace in the continued presence of oxalate,^{41,43} further Ca^{2+} being derived presumably from the extracellular fluid. This mechanism has been suggested to account at least in part for the hypocalcaemia encountered in association with the soft tissue precipitation of calcium oxalate in oxalic acid poisoning,⁶ and it is tempting to speculate that the finding of a serum calcium level of 1.26 mmol/l in the present case prior to dialysis, which is unusually low even for acute renal failure, may have had a similar basis.

After the injection of microspheres into the carotid artery of rhesus monkeys a high concentration was observed in the macular regions relative to the retinal periphery.⁴⁴ This greater vascularity of the submacular choroid has also been noted in man,⁴⁵ both blood pressure and flow being higher in this region.⁴⁴ As the evidence reviewed in this article indicates that both calcium and oxalate are blood-borne, we felt that the selective involvement

of the macular region and ciliary body, in the absence of local biochemical factors, simply reflects the high vascularity of these 2 regions.

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Eye manifestations in medullary carcinoma of the thyroid

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SUMMARY Multiple endocrine adenomatosis type III (MEA—III) in a 32-year-old white woman is reported. The initial manifestation, a thyroid nodule, was detected at the age of 4 years. The characteristic ocular manifestation of MEA—III are discussed.

We report an interesting case of multiple endocrine adenomatosis type III (MEA—III), in a 32-year-old white woman in whom the initial manifestation, a thyroid nodule, was detected at the age of 4 years. The characteristic ocular manifestations of MEA—III will be discussed as well as the role of the ophthalmologist in the early diagnosis of this syndrome.

Case history

The patient was a 32-year-old white woman. In 1951, when she was 4 years old, her mother noted a lump in her neck which was subsequently diagnosed as a nodule in the left lobe of her thyroid gland. Repeated physical examinations over the ensuing years revealed many signs involving different systems, eventually suggesting the presence of a complex syndrome. These included prognathism, thick lips, poor dentition, a large tongue with multiple marginal nodules, multiple polyps of the vocal cords, and a marfanoid habitus with long extremities, arachnodactyly, hyperextensibility, and increased laxity of the joints. In 1961 and 1962 she had operations for slipped right and left femoral epiphyses. She also suffered from recurrent bouts of severe diarrhoea.

Laboratory investigations during these years showed no thyroid dysfunction, a normal sella turcica, and normal levels of growth hormone.

In 1966 an excisional biopsy of the thyroid nodule was performed and histopathologically was diagnosed as Hurtle-cell carcinoma. This was followed by a total thyroidectomy. A later review of these pathological specimens established the correct

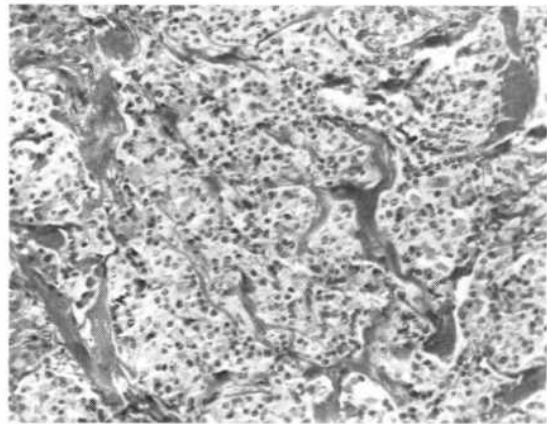


Fig. 1 Histopathology of medullary carcinoma of the thyroid. Parafollicular cells and stromal amyloid ($\times 18$).

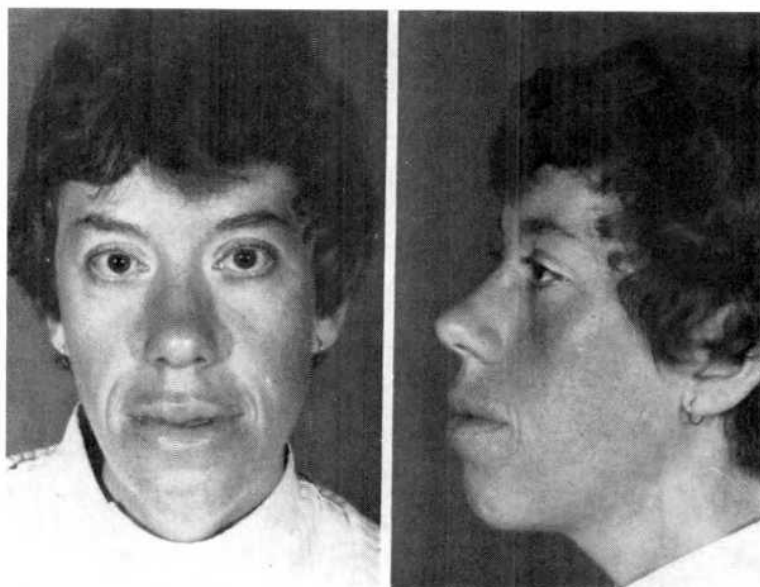
diagnosis of medullary carcinoma of the thyroid gland (Fig. 1). Once this diagnosis was established, investigations were carried out to check for other manifestations of multiple endocrine neoplasia. Our patient showed an absence of flare reflex after intradermal histamine test, normal serum calcium, and an absence of pheochromocytomas. There was no relevant family history. In 1967 mandibular osteotomies and dental repair operations were carried out, though residual prognathism remained (Fig. 2). A tongue nodule was also biopsied and it displayed the typical histopathology of a neuroma (Fig. 3).

In 1971 an enlarged cervical lymph node, noted on a routine examination, was excised, and it was negative for metastatic disease. A chest x-ray, skeletal survey, and serum calcium levels were again normal, suggesting that there were no metastases.

We first examined the patient in 1973. The visual

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Fig. 2 Thick lips and residual prognathism following mandibular osteotomies.



acuity was normal in both eyes. She had thick everted lid margins with anterior displacement of the cilia and ectropion puncti. The conjunctival edge of the lid margins was studded with small

irregular nodules (Fig. 4), and the bulbar conjunctiva contained diffuse swellings superior to the limbus bilaterally. There were bilateral thickened opaque corneal nerve fibres (Fig. 5). The patient also had dry eyes bilaterally as determined by repeated Schirmers testing. Excisional biopsies of both the conjunctival nodules on the lid margins and the superior bulbar swellings displayed the typical histopathology of plexiform neuromas (Fig. 6).

For several years she complained of occasional episodes of palpitations and sweating, though she never had any recorded hypertension. In 1976 pheochromocytomas were diagnosed by raised 24-hour urinary vanillyl mandelic acid (VMA) test

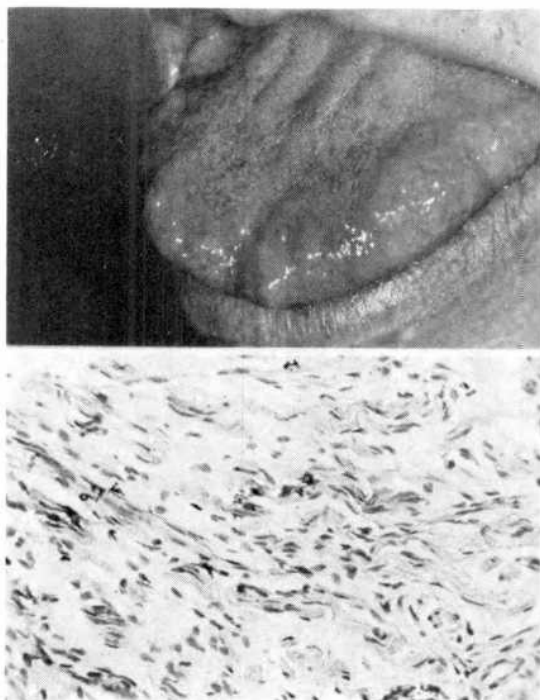


Fig. 3 Marginal nodules of the tongue. Histopathology of a tongue nodule showing a typical neuroma ($\times 34$).

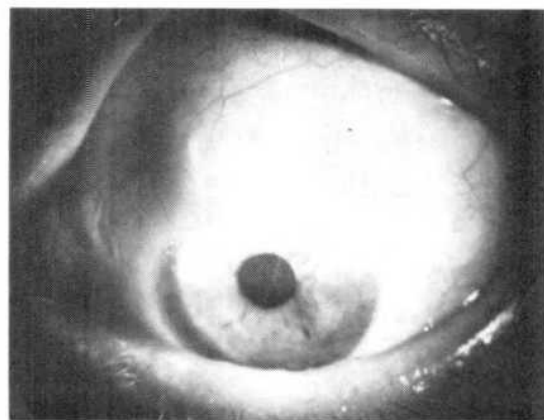


Fig. 4 Thickened lid margin with multiple nodular irregularities on the conjunctival edge.

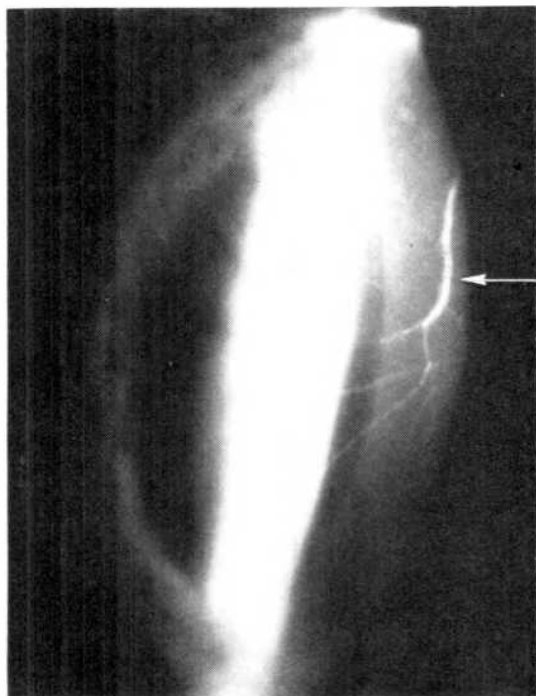


Fig. 5 Slit-lamp photograph showing thickened opaque corneal nerves.

and by a positive glucagon test. Adrenal venography confirmed the presence of a moderate sized tumour of the left adrenal and a possible abnormality of the right. In 1977 she underwent bilateral adrenalectomy and a cholecystectomy. The right adrenal contained a small pheochromocytoma while the left was markedly enlarged with this tumour. The gall bladder contained numerous calculi, and histopathologically there was a gangliomatosis of the gall bladder wall.

Discussion

The term multiple endocrine neoplasia (MEN) has been used since 1932, although Sipple¹ in 1961 first established the association between familial medullary carcinoma of the thyroid and pheochromocytomas. Later Steiner² divided MEN into types I and II, and Gorlin³ subdivided type II into A and B. Then in 1975 Khairi⁴ suggested that type IIB be called type III. Finally the term multiple endocrine adenomatosis (MEA) was suggested as a better term for this group of syndromes.

Pertinent features of these 3 syndromes are as follows.⁵

MEA—type I (Wermer's syndrome). Acidophilic and chromophobic adenomas of the pituitary gland,

functioning islet-cell tumours of the pancreas, adenomas of the parathyroid and adrenal cortex, and intractable peptic ulcer. Ocular symptoms are secondary to the pituitary tumours.

MEA—type II (Sipple's syndrome). Medullary carcinoma of the thyroid, pheochromocytomas, and parathyroid hyperplasia and adenomas.

MEA—I and II are two genetically distinct tumour endocrinopathies which both show autosomal dominant inheritance, and little overlap exists between them. MEA—II appears to be a form of neuroectodermal dysplasia, and the pheochromocytomas are of neural crest origin. A substantial body of evidence supports a similar derivation for the parafollicular cells (C cells) of the thyroid. A variant of MEA—II is the association of mucosal neuromas, which are also derivatives of the neural crest. This variant is designated by some authors as MEA—IIB and by others as MEA—III. Most cases with associated multiple mucosal neuromas are reported to be sporadic.

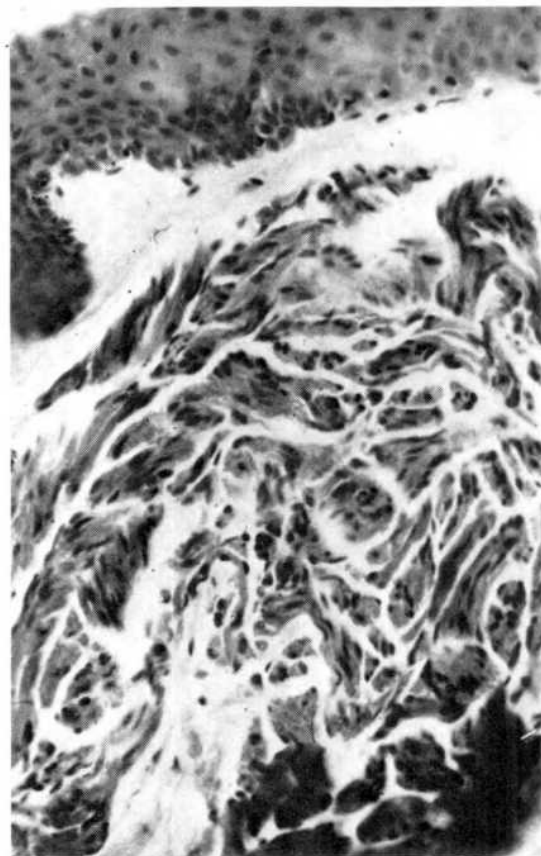


Fig. 6 Histopathology of a plexiform neuroma of the bulbar conjunctiva ($\times 40$).

MEA—III. Medullary carcinoma of the thyroid, parathyroid usually normal or hyperplastic, pheochromocytomas, multiple mucosal neuromas and skeletal manifestations suggestive of Marfan's syndrome. Ophthalmic findings include multiple neuromas of the lids and conjunctivae, dry eyes, and opaque nerves of the cornea. Patients have characteristic facies due to thick patulous lips, soft tissue prognathism, and large tongues studded with multiple nodules (neuromas).

Our case represents a MEA—III syndrome in which there was no family history. It is interesting that the thyroid nodule was first detected at age 4, at which time the clinical pathological entity of medullary carcinoma of the thyroid was not yet established. Only in 1959 did Hazard *et al.*⁶ differentiate medullary carcinoma from other types of thyroid carcinoma by the presence of stromal amyloid. The origin of medullary carcinoma has been established to be the parafollicular cells (C cells), which are the calcitonin-secreting cells. Calcitonin studies are therefore diagnostic and are mandatory in any individual with suspected medullary carcinoma of the thyroid. Detailed descriptions of the systemic, ocular, and laboratory features of this syndrome have been previously reported.⁷⁻⁹

Pheochromocytomas are not a constant feature of this syndrome (MEA—III) but are present in 37% of cases.¹⁰ They are more a feature of the familial dominantly inherited cases and are often bilateral. Interestingly, in our patient bilateral pheochromocytomas were diagnosed 28 years after her initial investigation of this syndrome.

Medullary carcinomas of the thyroid are of low grade malignancy. Our patient has been observed since 1951, when her thyroid nodule was discovered, and there have been no metastases. It has been reported that lymph node metastases do occur in 48–70% of cases.

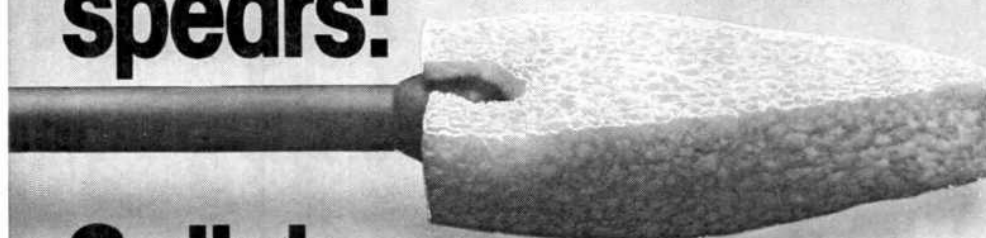
Mucocutaneous neuromas are an integral feature of 'multiple endocrine adenomatosis' type III. Ophthalmologically these neuromas occur as convoluted swellings or nodules of the bulbar and palpebral conjunctiva. The many nodular neuromas

of the palpebral conjunctiva may thicken the lid margins and cause anterior displacement of the lashes and ectropion puncti. Involvement of the corneal nerves results in thick opaque nerve fibres.¹¹ Dry eyes are frequently reported and are supposedly due to inadequate autonomic innervation. Our patient showed all these characteristics. Detection of these ocular signs by the ophthalmologist may provide the only clue to the diagnosis of an otherwise asymptomatic medullary carcinoma of the thyroid.

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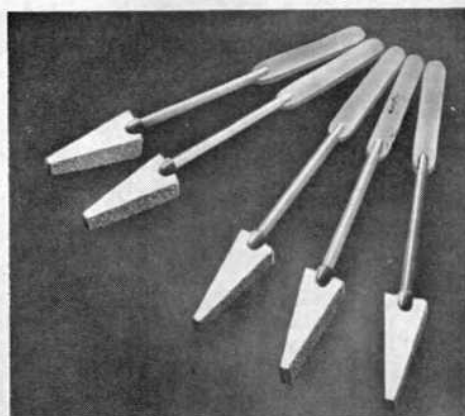


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Ocular reticulum cell sarcoma

JOHN W. SIMON AND ALAN H. FRIEDMAN

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SUMMARY Although rare, ocular reticulum cell sarcoma presents a recognisable clinical pattern, as confirmed by 3 new cases. Typical patients, in their sixth and seventh decades, initially complain of gradual visual loss. Examination reveals 'uveitis' with prominent vitreous debris and/or chorio-retinal infiltrative lesions. Topical steroid and mydriatic therapy is ineffective. Reticulum cell sarcoma in the central nervous or other systems may precede or accompany the ophthalmic presentation. In an increasing number of cases tissue diagnosis and effective therapy have followed vitreous aspiration.

Reticulum cell sarcoma or, as reclassified by Rappaport,¹ histiocytic lymphoma, is a malignancy composed of large cells resembling histiocytes. Its origin, which may be single or multicentric, is usually within the reticuloendothelial system—chiefly lymph nodes—or in the central nervous system (CNS), where it is often referred to as microglioma. Precise definition of the cell of origin, its immunological markers, the relationship between the disease and other non-Hodgkin's lymphomas, and its aetiology have all eluded researchers.² However, dramatic progress has been attained recently in treatment. Chemotherapeutic remissions 'tantamount to cure' have been achieved in 41% of patients with the most advanced stages of disease.³ Localised involvement is treated with radiation, either alone or in conjunction with chemotherapy, with even greater success.³

Ocular involvement in reticulum cell sarcoma is rare, with only 25 histologically proved cases in the world literature. Until recently examination of enucleated specimens was required for diagnosis. More frequent reports during the past 10 years have demonstrated a recognisable ophthalmic presentation, typically as a refractory uveitis in middle-aged patients. Vitrectomy has provided a relatively noninvasive, and in many cases the only available, source for tissue diagnosis.⁴ As outlined below, treatment of affected eyes, which were previously doomed, has resulted in rewarding local cures.

In this article we describe the clinical and pathological findings in 3 new cases of reticulum cell

sarcoma involving the eye. The literature is reviewed with particular reference to defining further the early ophthalmic manifestations of the disease.

Case reports

CASE 1

A 66-year-old white man was seen in April 1979 because of gradual visual loss in both eyes, left more than right, during the previous 6 weeks. Past medical history included gout, controlled by diet, acute myocardial infarction in 1976, and diabetes mellitus treated with diet and oral hypoglycaemic drugs. Examination was essentially negative. Ophthalmic examination showed corrected visual acuities of 6/140 right eye and 6/60 left eye. Corrected near acuities were J2 right eye, and J10 left eye. Applanation tensions were 16 and 18 mmHg respectively. Ocular motility was full and the lids were normal. The anterior segments were unremarkable with the exception of trace cell and flare bilaterally. There was 1+ nuclear sclerosis of both lenses. Pupils were equal and reactive. In the right eye the vitreous contained 2+ cells with a posterior vitreous detachment and additional cells collected on the posterior vitreous face. In the left eye there were approximately 3+ vitreous cells with more confluent precipitates on the detached posterior vitreous face. The discs were normal, but throughout the fundus there were many focal yellow-white subretinal lesions with surrounding retinal haemorrhages (Fig. 1).

The patient was admitted to the hospital. A and B scan ultrasonography performed in both eyes showed the posterior vitreous detachments with a membrane-like formation extending from the region of the disc to the vitreous base (Fig. 2). Fluorescein

Correspondence to Alan H. Friedman, MD, Department of Ophthalmology, Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY 10029, USA.



Fig. 1 Case 1. Clinical photograph, left eye, showing retinal and subretinal infiltrates and retinal haemorrhages. Moderate vitreous haze precludes clear view.

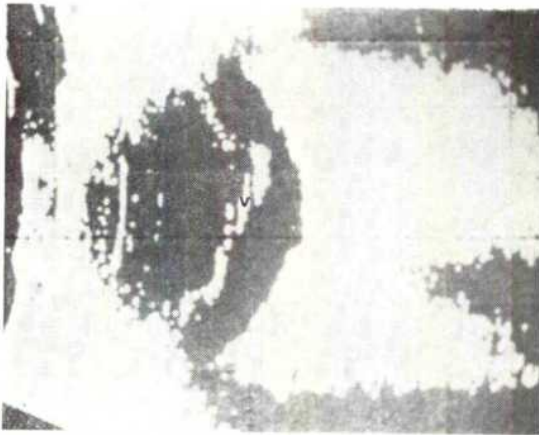


Fig. 2 Case 1. B scan ultrasound, left eye, showing detachment and thickening of posterior vitreous face (V).

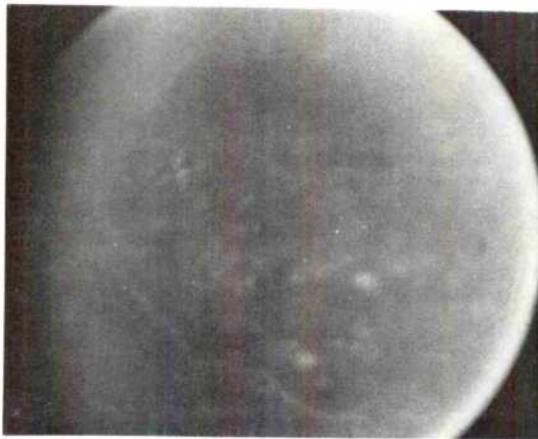


Fig. 3 Case 1. Fluorescein angiogram, right eye, showing subpigment epithelial infiltrates and leakage.

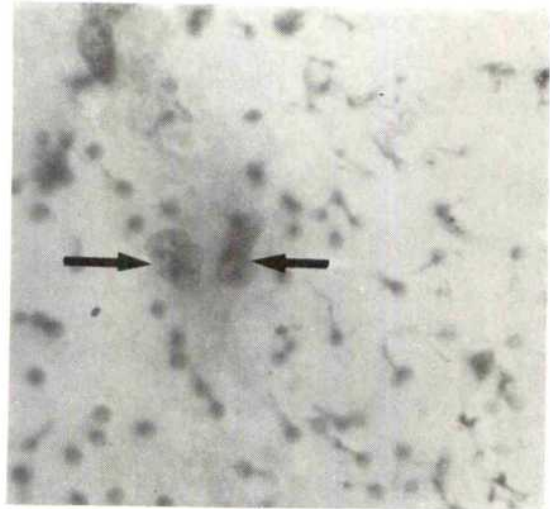


Fig. 4 Case 1. Photomicrograph of vitreous aspirate, left eye, demonstrating characteristic cells of reticulum cell sarcoma (arrows). (Giemsa, $\times 980$).

angiography showed the presence of subpigment epithelial infiltrates with diffuse leakage in later shots (Fig. 3). Physical examination and routine laboratory studies were within normal limits except for a mildly raised blood sugar. Titres for toxoplasmosis, candida, and cytomegalovirus were negative. A vitreous aspiration was performed in the left eye with the Ocutome. The material collected was cytocentrifuged, spread on slides, stained, and examined.

Cytological examination revealed many large cells with ill-defined cell borders and large pale oval-shaped nuclei. Many nuclei were multilobulated, and some contained a distinct basophilic nucleolus. Moderate pleomorphism was present, with occasional finger-like projections of the nuclei (Fig. 4). A diagnosis of reticulum cell sarcoma of the vitreous was made. Neurological examination and computerised tomography revealed no evidence of CNS disease. The patient was put on 80 mg of prednisone daily by mouth. Over the ensuing 2 weeks there was a gradual improvement in vision to the level of 6/7 right eye and 6/8 left eye. The patient has been maintained on prednisone, 40 mg daily, and the vision has remained stable. The vitreous infiltration has cleared, and there is a marked clearing of the subretinal pigment epithelial infiltrates. In these areas there have been some pigment epithelial migration and proliferation.

CASE 2

A 77-year-old white female was first seen in November 1976 with a history of blurred vision in the left

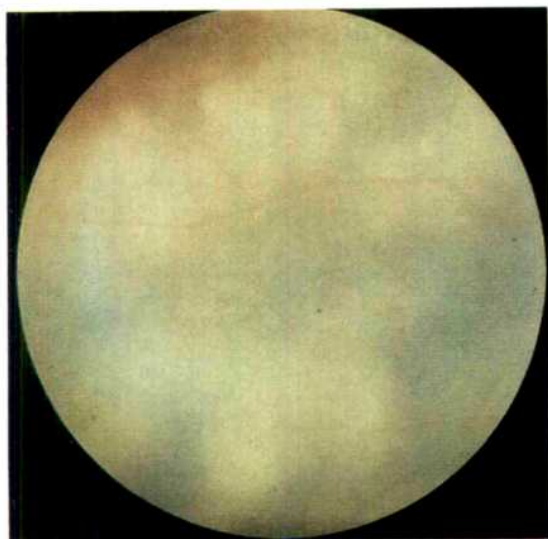


Fig. 5 Case 2. Clinical photograph, left eye, showing subretinal infiltrates and vitreous haze.

eye of 2 weeks' duration. An ophthalmic examination showed corrected visual acuities of 6/21 right eye and 6/120 left eye. Ocular motility was normal. Intraocular pressures were 18 mmHg bilaterally. Slit-lamp examination revealed normal anterior segments with mild nuclear sclerosis bilaterally. The vitreous contained a moderate cellular infiltration, and in the right fundus there was a small exudate just outside the inferotemporal arcade. These deposits were at the level of the retinal pigment epithelium. In the left fundus, adjacent to the superior temporal retinal vessels and just superior to the macula, was a white fluffy lesion of approximately 3 to 4 disc diameters which also had the appearance of an infiltrate at the level of the retinal pigment epithelium. There were scattered haemorrhages at the superior edge of this lesion and marked macular oedema (Fig. 5). General physical examination, complete blood count, urine analysis, and results of liver chemical tests were within normal limits. A chest x-ray was negative, as were serological tests for toxoplasmosis, cytomegalovirus, and candida.

The patient was put on 40 mg of prednisone for 10 days, by which time visual acuity in the left eye had improved to 6/60. There were some pigmentary changes of the retinal pigment epithelium in the region of the inflammatory focus in the left eye. Approximately 2 weeks later the patient became confused and complained of increased blurring of vision. Examination of the left eye revealed a studding of the retina with pale yellow-white exudates obscuring overlying retinal detail. Fluorescein

angiography of the left eye suggested lesions at the level of the retinal pigment epithelium.

The patient was continued on corticosteroids, but by January 1977 the lesions had progressed. In the left eye the vitreous was markedly hazy, and vision had dropped to light perception. The patient was admitted to the hospital. A general medical examination was again entirely negative. Computerised tomography revealed a large mass in the region of the splenium of the corpus callosum. It could not be determined whether the lesion was metastatic or lymphomatous in origin. During the course of the examination the patient became increasingly disorientated and died on the tenth day in hospital. The eyes were enucleated post mortem.

Gross and microscopic examination of the right eye gave normal results. Gross examination of the left eye revealed a large amount of opaque material with haemorrhages in the vitreous. A zone encompassed by the superior temporal and inferior temporal vessels contained marked retinal thickening and opacification. There were several haemorrhages in the surrounding area. Microscopic examination revealed a normal cornea and anterior chamber. The iris and ciliary body contained a light infiltrate of inflammatory cells, chiefly lymphocytes. There was early posterior migration of the lens epithelium. Within the vitreous body, which was detached, were a moderate amount of degenerating blood and necrotic cells, some of which were identified as histiocytes. There was a massive chorioretinal lesion corresponding to the abnormality noted posteriorly on gross examination. Throughout this area the retinal pigment epithelium and Bruch's membrane had been destroyed and the retina had degenerated. Scattered infiltrates in the subretinal pigment epithelial zone contained abnormal histiocytes (Fig. 6). Many had pale nuclei with coarse clumped chromatin. There were abundant mitotic figures, and many nuclei were multilobulated. In the overlying retina were large amounts of extravasated blood and severe cystoid degeneration. A preretinal glial membrane was present. The choroid contained patchy prominent collections of lymphocytes and histiocytes, many of which were abnormal. There were no viral inclusion bodies, and no micro-organisms could be identified with fungal and bacterial stains. Cross-sections of the optic nerve showed degenerative changes of the nerve fibres. Necropsy confirmed the presence of reticulum cell sarcoma involving the central nervous system.

CASE 3

A 68-year-old woman was seen approximately 2 years after uneventful cataract extraction. At that time she complained of progressive loss of vision

in both eyes. Ophthalmic examination revealed finger counting vision right eye and 6/120 left eye. Intraocular pressures were 16 mmHg in each eye. Ocular motility was full. The anterior segments were normal except for the presence of bilateral peripheral iridectomies and evidence of previous cataract extraction. A general medical examination and routine laboratory data were within normal limits. The patient underwent vitrectomy, first right

eye and then left eye, with approximately 4 to 5 months between the operations. The material collected was not studied for cytology but was cultured for fungi and bacteria. These cultures were negative. Postoperatively the patient's vision was 6/9 in each eye. During the course of the next 9 months she became progressively disorientated and obtunded. She was admitted to hospital in a coma and died without a definitive diagnosis. A general necropsy was refused, but the family granted permission for examination of the eyes.

Gross examination revealed 2 similar eyes. Lenses were absent, and there were peripheral iridectomies. Opening the eyes revealed a layering of thick white material on the pars plana for 360° in each eye (Fig. 7). The material had the consistency of sour cream. The central vitreous was clear and liquified. The optic nerve and retina posteriorly in each eye were unremarkable. Histopathological examination was similar bilaterally. Anterior segments were normal. Lying on the surface of the pars plana was a diffuse vitreal infiltration with abnormal histiocytes (Fig. 8). The tumour cells contained oval nuclei with prominent nucleoli and a thick rim of dark blue cytoplasm. The cells were highly pleomorphic, and there were abundant mitotic figures. A diagnosis of reticulum cell sarcoma was made.

Discussion

By all accounts intraocular reticulum cell sarcoma is unusual. Allen and Straatsma,⁵ in their review of 76 patients with leukaemia and allied disorders, discovered no ocular involvement among 10 cases of malignant lymphoma. In 2 separate reviews a total of 88 patients with orbital lymphomas included only 4 with intraocular disease.^{6,7}

Cooper and Riker⁸ presented the first case of ocular reticulum cell sarcoma; 47 additional cases have been reported to date. Of these, approximately half are considered primary—that is, the disease was either limited to the eye or appeared extraocularly long after an ophthalmic presentation. Two patients who came to necropsy with no history of specific therapy were found to have only eye involvement, providing strong evidence for an ocular origin of the disorder. Secondary cases, presumably including some with multicentric origins, are those with associated CNS or systemic presentations. Although the lymph node and visceral form is by far the more common, eye involvement is more frequent in the CNS form. Neault *et al.*⁹ found an associated 'uveitis' in 7 of 17 patients who underwent craniotomy for CNS reticulum cell sarcoma. Our 3 cases are all primary; 2 eventually had CNS

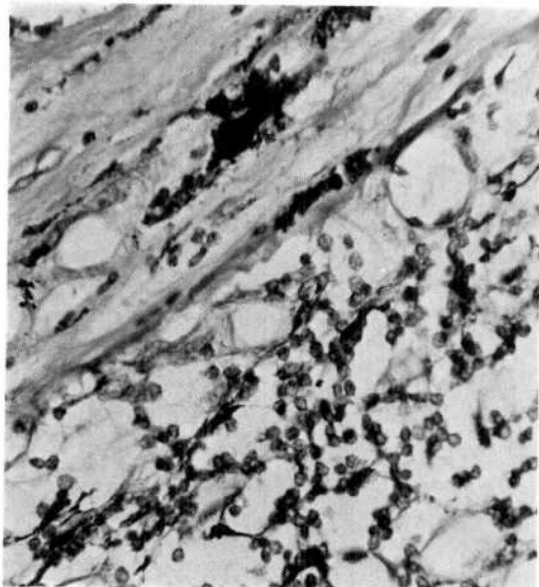


Fig. 6 Case 2. Photomicrograph, left eye, showing abnormal reticulum cells in subpigment epithelial space. (Haematoxylin and eosin, $\times 400$).

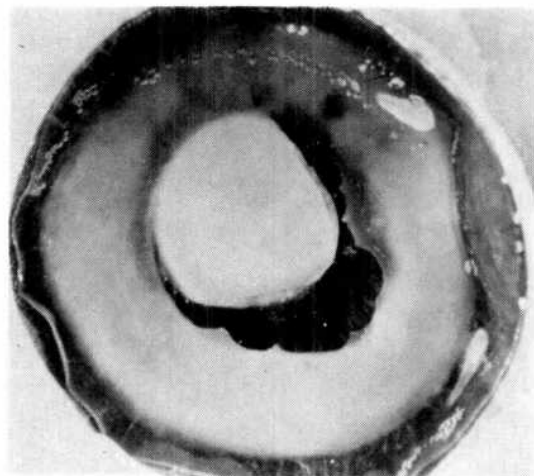


Fig. 7 Case 3. Opened globe viewed posteriorly showing layering of white material on pars plana.

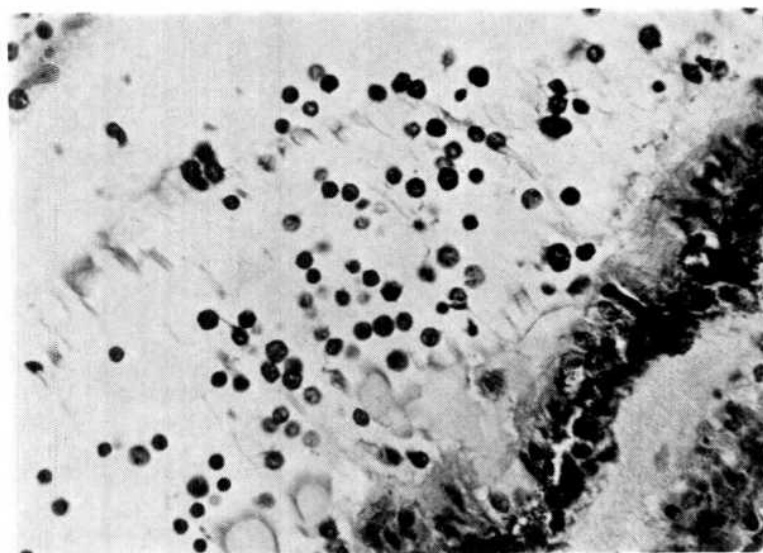


Fig. 8 Case 4. Photomicrograph of area shown in Fig. 7, showing characteristic tumour cells on pars plana. (Haematoxylin and eosin, $\times 420$).

manifestations without clinical evidence of systemic disease.

Patients have been typically in their sixth and seventh decades at the time of presentation. The first report was of a 27-year-old man, and 1 patient was 81. These are exceptions, however, and the mean age is 64. There is no discernible sex predilection among reported cases despite a male: female ratio of 2:1 in cerebral reticulum cell sarcoma.¹⁰ Three patients are identified as blacks, roughly in proportion to the general population.

Ophthalmic consultation was sought in most cases because of decreased visual acuity. One patient initially described floaters, and a second complained of photopsia.¹¹ The principal finding, almost without exception, was debris which appeared inflammatory—variable in location and extent, but generally refractory to topical steroid therapy. Both eyes were involved in roughly 50% of cases, though asymmetry is typical.¹⁰ One patient¹² presented with a hypopyon; more typically, anterior segment reaction resembled a mild, nongranulomatous iritis, with or without keratic precipitates.

It was in the posterior segment that the disorder presented most characteristic findings. In slightly more than half of cases, fundus lesions resembling retinal or subretinal infiltrates were noted. Involved retina is described as white and thickened, with surrounding haemorrhage.⁴ Some observers have depicted the lesions as patchy, yellow-white to greenish-grey in colour, with fluffy outlines that rapidly become confluent.¹³ Encroachment of the lesions on optic nerve or macula rapidly diminished visual acuity. Vitreous involvement typically accom-

panied fundus lesions but occasionally was seen alone. It has been variously described as inflammatory cells, debris, or veils—often dense enough to obscure underlying retinal detail.⁴

Secondary glaucoma accompanied intraocular reticulum cell sarcoma in approximately half the cases.¹² In 4 of 17 cases¹⁴ the mechanism was rubeosis iridis and neovascular angle closure. Increased intraocular pressure has more typically been related to cellular debris and synechial closure in the anterior chamber angle. Glaucoma was not seen in our 3 cases. In other respects, however, they confirm the typical clinical presentation: patients in their 60s and 70s whose decreased acuity was ascribed to 'uveitis' wherein vitreous debris and/or chorioretinal infiltrative lesions were prominent features. In all 3 cases topical steroid and mydriatic therapy was ineffective. The diagnosis is even more suggested when there is evidence of CNS or systemic reticulum cell sarcoma.

The pathological data in our cases likewise typify the ocular involvement in this disease. Interestingly, the inflammatory component on histological examination is as prominent as in the clinical setting. In at least 1 case¹⁵ a patient with bilateral posterior uveitis was found at necropsy to have neoplastic changes confined to the choroid and retina of one eye. Choroidal lesions and vitreous debris noted before death in the fellow eye represented infiltrations of chronic inflammatory cells.

The tumour cells are indistinguishable from those of reticulum cell sarcoma elsewhere or microglioma in the CNS. They are large and pleomorphic, with scant cytoplasm and prominent nuclear membranes.

Nuclei are round or oval, occasionally multiple, and with frequent mitoses, clumped chromatin, and prominent nucleoli. Immunoperoxidase staining has been used to demonstrate a B cell origin, though post-mortem changes may interfere with results,¹⁰ and the cell or origin remains in doubt.¹⁴ Reticulum cells are present in normal choroid, and microglia are normal retinal constituents.⁴

On microscopic examination retinal involvement is most commonly seen. In retina as in brain tissue the cells follow a perivascular distribution, often surrounded by fine reticulum fibres which stain with silver and give the tumour its name. In the uveal tract cells tend to infiltrate more diffusely, forming dense placoid masses.¹³ An unusual characteristic of the tumour is its capacity to break through Bruch's membrane, forming discrete masses beneath the retinal pigment epithelium.¹² Exudative retinal detachment and vitreous haemorrhage have followed; papilloedema has occurred with infiltration of the optic disc.¹⁶

Retinal and uveal lesions may occur separately or together. Vitreous debris may accompany either or, as in our case 3, may occur alone.^{11 14 16} Several authors have traced a trend for CNS disease to coexist with retinal involvement, whereas 'pure' uveal infiltration occurs more frequently with systemic disease.

Other entities may produce similar white retinal lesions and must be distinguished from reticulum cell sarcoma. Retinal metastases are exceedingly rare and are generally found in the terminal stages of widespread disease. Leukaemic infiltrates and retinitis secondary to bacterial or fungal sepsis are more common but can be readily diagnosed with bone marrow or blood studies. Similarly, toxoplasmosis and cytomegalovirus infection can be differentiated with high, or ideally rising, serum titres. Cotton-wool spots are generally seen in association with systemic hypertension or collagen vascular disease, have more sharply defined borders, and are unaccompanied by other signs of inflammation.

Tissue diagnosis is a prerequisite for the initiation of therapy in reticulum cell sarcoma. Systemic disease is diagnosed by biopsy of involved lymph nodes, bone marrow, spleen, or other viscera; in the CNS examination of the cerebrospinal fluid has circumvented the necessity for craniotomy in some cases. Ocular involvement has usually been diagnosed post mortem, though in 7 cases diagnoses were made after enucleation of blind, painful eyes. In 1 case diagnosis followed biopsy of a subcutaneous lid lesion.¹² Most notable are the 3 cases previously reported,^{1 11} to which we add our case 1, in which diagnosis came from examination of vitrectomy specimens from visually intact eyes. In

each case vitrectomy improved visual acuity, if only transiently.

Radiation therapy has proved especially efficacious in affected eyes. So far 8 cases have been reported in which eyes were irradiated with appropriate shielding. In 6 treatment resulted in shrinkage of chorioretinal lesions, clearing of vitreous debris, and permanent improvement in visual acuity. Chemotherapy has produced somewhat less impressive results in cases of eye involvement, though treatment regimens have varied.^{12 17} A mass in the ciliary body responded dramatically to procarbazine, lomustine and vincristine in the only case in which therapy approximated to that now recommended.^{2 14}

Barr *et al.* noted¹² that of 14 patients with primary intraocular reticulum cell sarcoma 9 eventually developed CNS or systemic involvement. Since approximately half of all cases with eye findings present with eye symptoms, it is to be hoped that early diagnosis with vitrectomy may make possible earlier institution of specific systemic therapy in the future.

We are grateful to Miss Dinah G. Seibel for typing the manuscript and to Messrs Robert Campanile and Howard Radzyner for preparing the photographs. We are indebted to Dr W. Richard Green for reviewing the vitreous aspirate in case 1.

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Correspondence

Coloboma of optic nerve

SIR, In the June 1978 issue of the *BJO* (p. 347) I described the histopathology of a coloboma of the optic nerve which had simulated a tumour clinically. In citing the pertinent literature I overlooked a reference in the Czech literature which reported a similar case: Vrabec, J., Kolobóm vstupu zrakového Nervu, *Ceskoslovenská Oftalmologie*, 1971, **27**, 2.

DAVID G. COGAN

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Notes

Keeler fellowship

The Keeler fellowship for 1980-81 has been awarded to Dr T. A. S. Buchanan of the Department of Ophthalmology, Royal Victoria Hospital, Belfast. Dr Buchanan will spend a year as fellow in neuro-ophthalmology with Professor Hoyt at the University of California, San Francisco, commencing 1 August 1980.

Oculoplastic surgical dissection

A semiannual oculoplastic surgical dissection course will be held at Tarrytown, New York, under the sponsorship of New York Medical College, on 22-25 October 1980. Fee \$650. Further details from Ms P. Tamkin, c/o Dr P. Guibor, 630 Park Avenue, New York, NY 10021, USA.

Contact lens course

An annual course in contact lens technology will be held at the Cullen Eye Institute, Baylor College of Medicine, Houston, Texas, on 4-6 December 1980. Further details from Professor David Paton, Cullen Eye Institute, Baylor College of Medicine, 6501 Fannin (NC 200), Houston, Texas 77030, USA.

Intraocular lens implants

The International Intraocular Lens Implant Symposium will be held in Singapore on 27 January-1 February 1981. It is organised by the International Intraocular Implant Club, the Netherlands Intraocular Implant Club, and the United Kingdom Intraocular Implant Club. Participation is limited. Further details from the Organising Secretary, c/o Mt Elizabeth Travel Service Pte Ltd., Suite 107 1st Floor, Mt Elizabeth Medical Centre, Mt Elizabeth, Singapore 0922.

Ocular and adnexal tumours

A course on current thinking in the management of ocular and adnexal tumours will be held in San Francisco on 4-6 February 1981. Subjects to be discussed include masquerade syndromes; lid and conjunctival tumor management; controversies in the management of choroidal melanoma; iris tumors and ocular metastases; retinoblastoma; and advances in orbital tumor diagnosis and management. Further information from Dr Devron H. Char, School of Medicine, University of California, San Francisco, CA 94143, USA.

Toronto refresher course

The Department of Ophthalmology of the University of Toronto will hold its annual refresher day course on 6 and 7 February 1981. The guest speaker will be Dr A. J. Bron and the Walter Wright lecturer Dr Peter Laibson whose topic will be 'Corneal and External Diseases'. Further information from the Department of Ophthalmology, University of Toronto, 1 Spadina Crescent, Room 115, Toronto, Ontario, M5S 2J5, Canada.

Laser meeting

The Laser and Advanced Retinal Meeting will be held in Penang, Malaysia, on 1-5 March 1981. This meeting is organised by the International Agency for the Prevention of Blindness and the Ophthalmological Society of Malaysia. Participation is limited. Details from Dr Michael S. H. Oh, c/o Penang Medical Centre, 1 Jalan Pangkor, Penang, Malaysia.

Annual congress of Ophthalmological Society

The Ophthalmological Society of the United Kingdom will hold its Annual Congress next year at the University of Southampton Medical School on 8-10 April 1981. Further information from Miss M. M. Hallendorf, Ophthalmological Society of the United Kingdom, Royal College of Surgeons, 35-43 Lincoln's Inn Fields, London WC2A 3PN.

International congress of ophthalmology

The 24th International Congress of Ophthalmology will be held at San Francisco on 31 October to 5 November 1982. These meetings go back 125 years to the first congress held in Brussels. Their purpose is to bring together ophthalmologists to exchange new ideas and information in order to advance the treatment of eye diseases around the world. The Annual Meeting of the American Academy of Ophthalmology will be combined with the congress. Abstracts of papers, exhibits, or films must be received by 15 December 1981 on submission forms requested from Frederick C. Blodi, MD, ICO, Box 3030, San Francisco, California 94119, USA. Further information from Dr Bruce Spivey at the same address.

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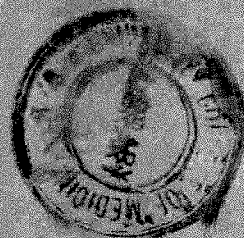
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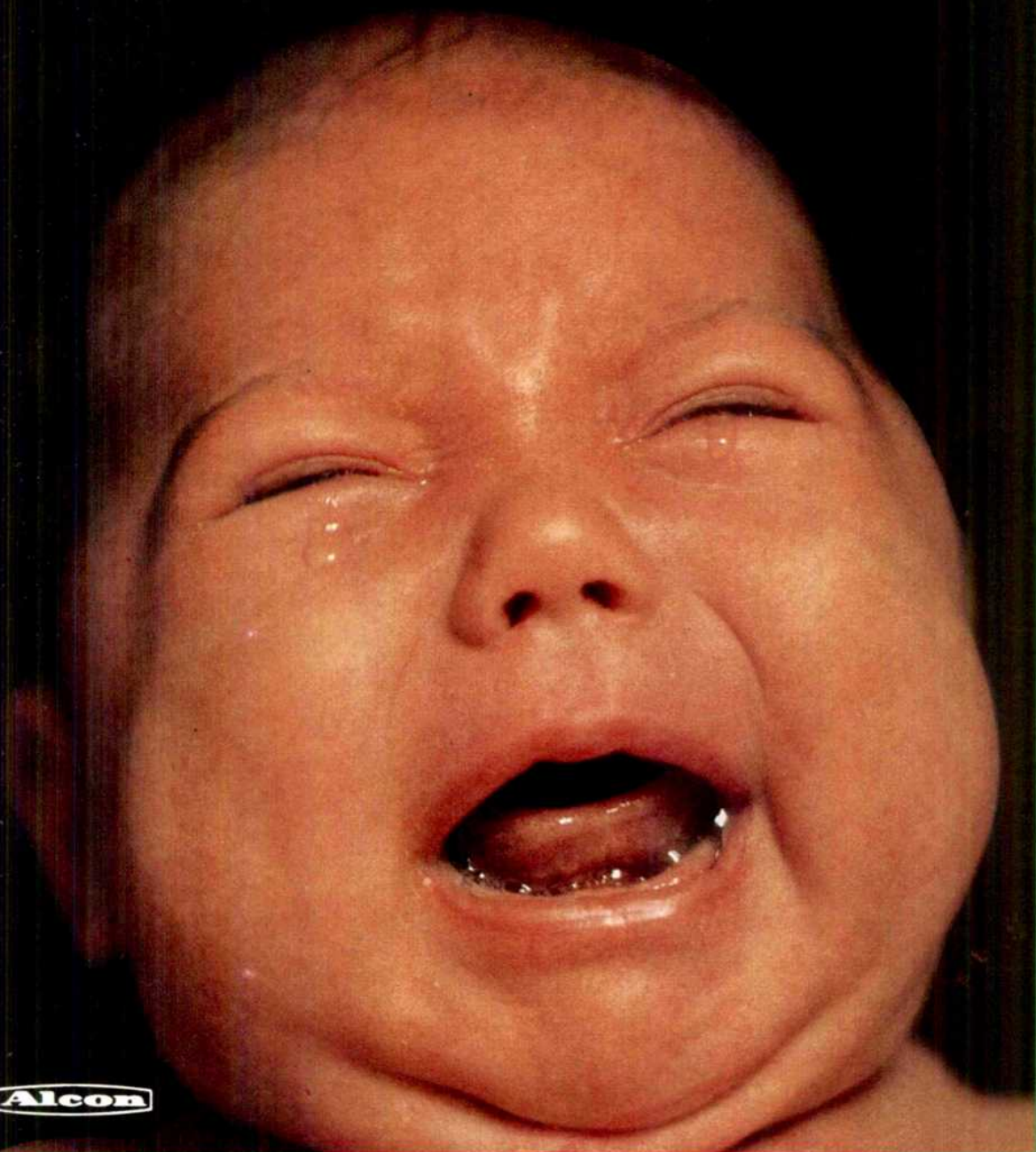
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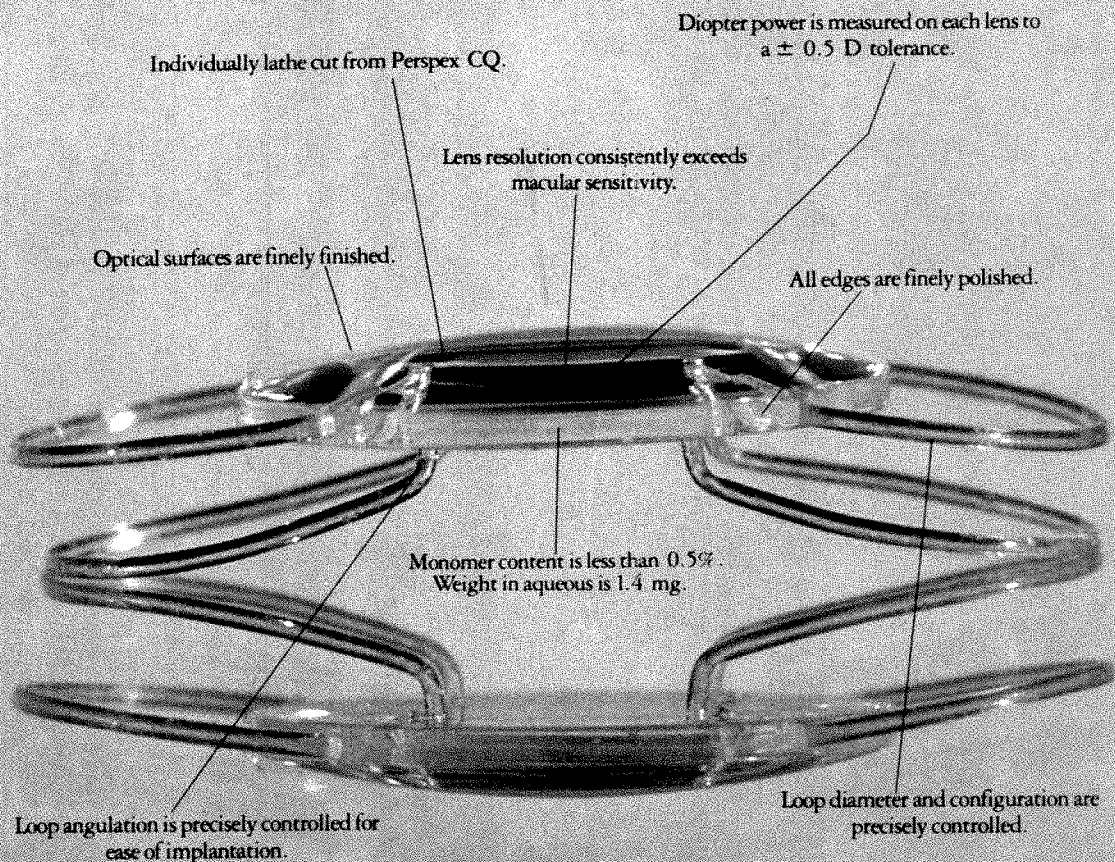
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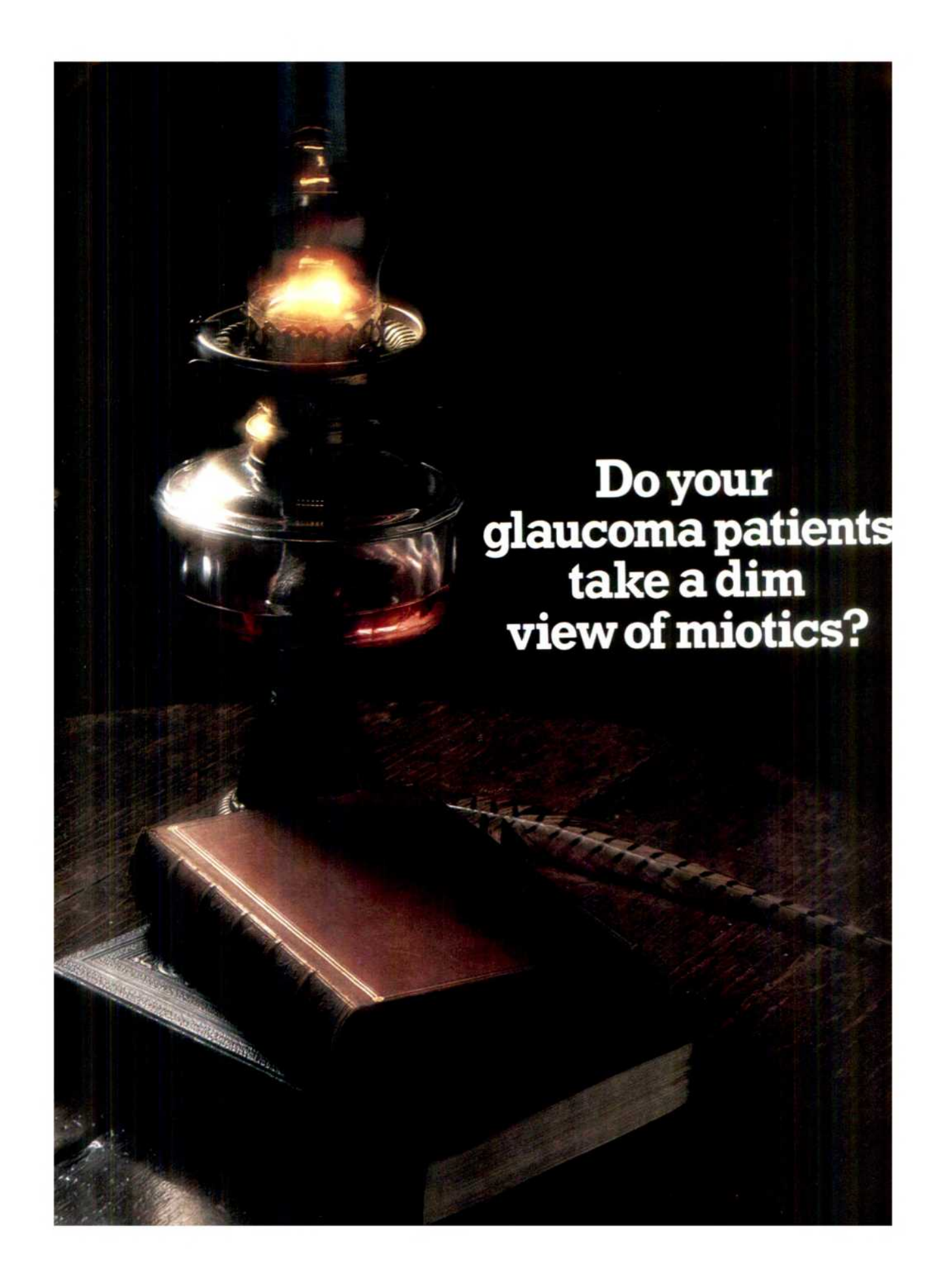
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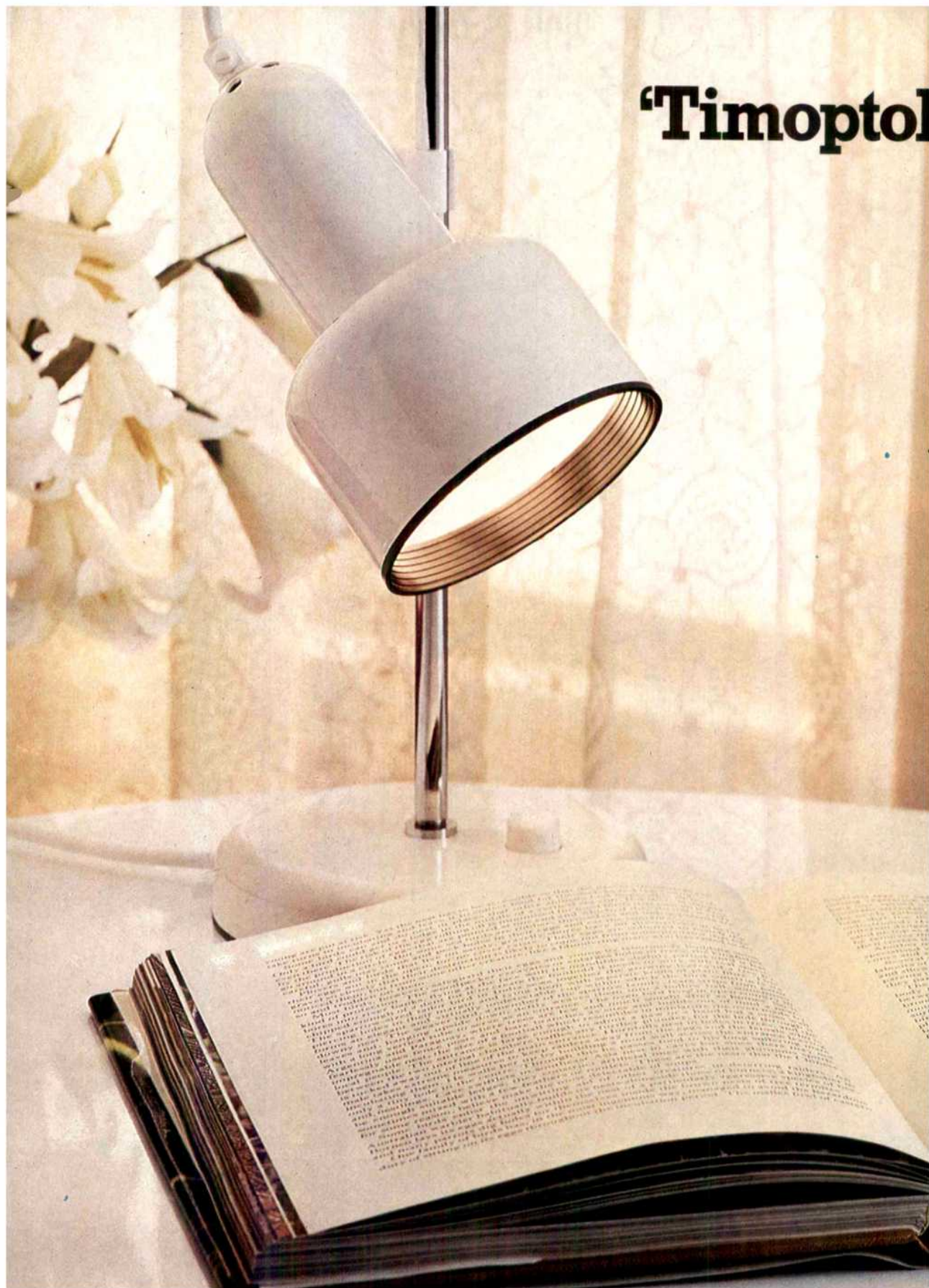


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Precautions Ophthalmic Solution TIMOPTOL should be used with caution in patients with known contra-indications to systemic use of beta-adrenergic-receptor blocking agents such as patients with bronchospastic disease, and congestive heart failure.

There have been reports of skin rashes and/or dry eyes associated with the use of systemically administered beta-adrenergic-receptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when treatment was withdrawn. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy involving the beta-blockade should be gradual.

Although TIMOPTOL has been used in a small number of patients wearing contact lenses made of polymethylmethacrylate (PMMA), and there have been no reports of adverse effects, at present, experience is too limited to enable a conclusion on safety to be made.

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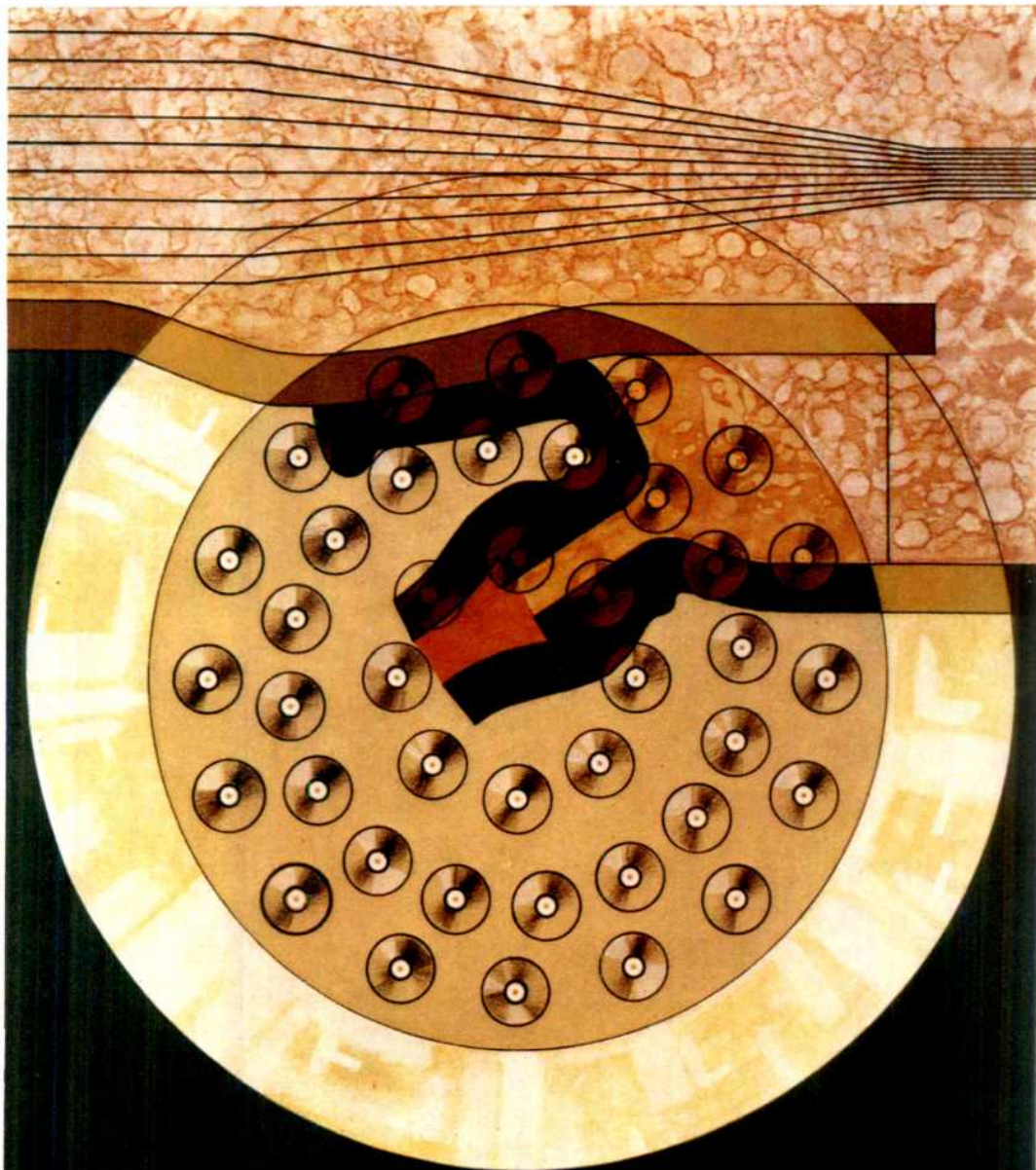
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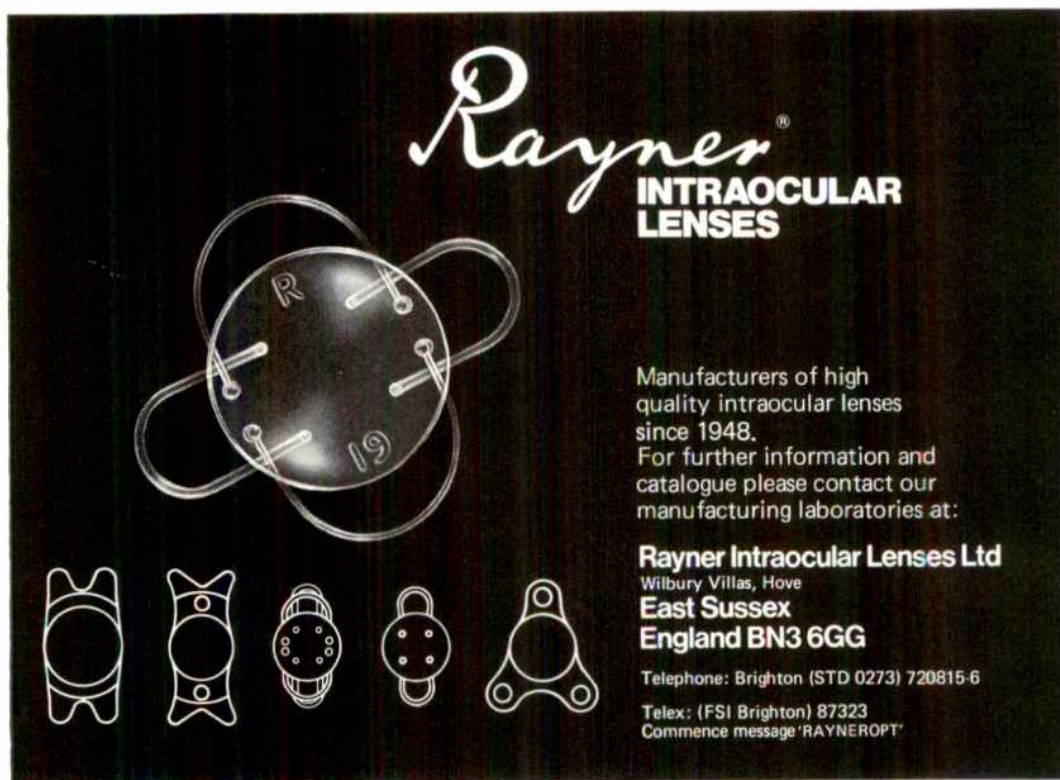
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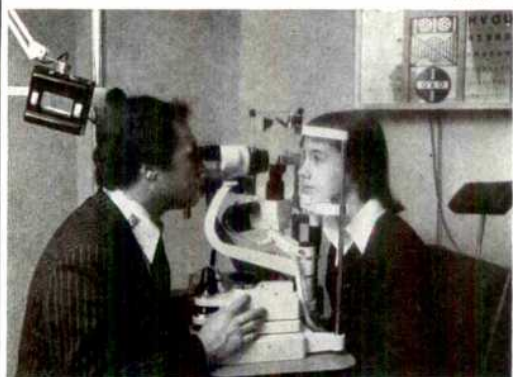
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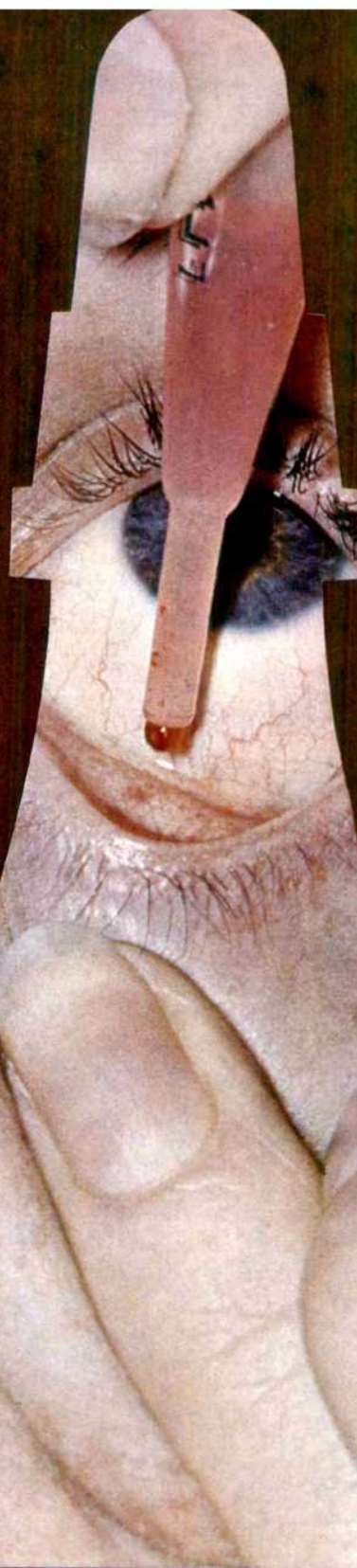
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Experimental posterior penetrating eye injury in the rhesus monkey: vitreous-lens admixture

PHILIP E. CLEARY, GLEN JARUS, AND STEPHEN J. RYAN

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SUMMARY A standardised experimental posterior penetrating eye injury in the rhesus monkey with the vitreous-lens admixture resulted in limited fibrous ingrowth from the wound and minimal traction on the peripheral retina. Microscopically inflammation was noted in the iris, ciliary body, and as a perivascular infiltrate of the inner retina. Periretinal membranes did not occur, and cellular proliferation within the vitreous was less marked than observed after an identical wound and simulated vitreous haemorrhage in previously reported studies. The lens may be a less important stimulus to intravitreal fibroblastic proliferation than previously assumed.

Penetrating ocular trauma remains an important cause of blindness, particularly among young, productive individuals.¹⁻⁴ In recent years the visual prognosis has improved markedly for penetrating injuries of the anterior segment of the eye. However, injuries involving the posterior segment continue to result frequently in a poor visual outcome.^{2,5-11} The principal reason for loss of vision after posterior injury is the development of retinal detachment,^{7,10,12,13} which may be rhegmatogenous or tractional.^{10,14} Posterior penetrating injuries of the eye characteristically develop traction retinal detachment.^{3,10}

The sequence leading to traction retinal detachment after a penetrating injury is characterised histologically by intravitreal fibrocellular proliferation forming cyclitic, transvitreal, epiretinal, and retroretinal membranes.^{13,15-17} Elements that may contribute to the fibrocellular response include the penetrating wound, vitreous haemorrhage, lens injury, trauma of the ciliary body, infection, or foreign bodies.^{12,13,15,18} Clinical studies have shown the significance of vitreous incarceration in the scleral wound and vitreous haemorrhage in the development of intravitreal fibrocellular proliferation and traction retinal detachment.^{4,7,18-20} Other studies have identified injury to the lens with vitreous-lens admixture as a potent stimulus to inflammation and cellular proliferation within the vitreous.^{10,15,18,21}

Because the laboratory environment allows more precise control of variables than a random patient population, we have developed an experimental animal model of a posterior penetrating eye injury in the rhesus monkey to analyse the importance of specific variables and to elucidate pathogenetic mechanisms. We have found this model useful in confirming the significance of vitreous haemorrhage and vitreous incarceration in the wound in posterior penetrating eye injuries and in demonstrating the pathophysiology of injury-induced traction retinal detachment.^{22,23} The model has also proved useful in assessing the role and timing of vitrectomy in the treatment of such injuries.²⁴ In the present study we have combined our standard penetrating injury with an injection of autologous lens material into the vitreous to examine, as an isolated variable, the effects of the lens-vitreous admixture.

Material and methods

Five rhesus monkeys weighing 5 to 7 kg, and of either sex, were anaesthetised by intravenous injection of sodium pentobarbital. The pupils were dilated with 1 drop of 1% cyclopentolate hydrochloride and 1 drop of 10% phenylephrine. The eyelids and surrounding skin were scrubbed with povidone-iodine solution, and the eyes were draped with sterile adhesive polyethylene drape. All surgery was performed under sterile conditions under an operating microscope.

In the right eye of each animal an intracapsular lens extraction was performed through a limbal

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incision. A muscle hook was used to rupture the zonular fibres and the lens was removed with a lens loop. A sector iridectomy and an anterior vitrectomy by means of the Ocutome were performed. The limbal incision was closed with interrupted 8-0 silk sutures.

The extracted lens was ground with a sterile mortar and pestle, and suspended in sterile Ringer's lactate solution for a total volume of 0.5 ml.

In the left eye of each animal a standard injury was performed, as previously described.²² An incision 8 mm long and 3.5 mm from the corneal-scleral limbus was made through the pars plana, avoiding the lens and the peripheral retina. Pro-lapsed vitreous was excised and the wound carefully closed with interrupted sutures of 8-0 silk by microsurgical techniques. After wound closure the fundus was inspected by indirect ophthalmoscopy, and the areas of the wound and peripheral retina were examined by scleral indentation to exclude any eye with vitreous haemorrhage or damaged retina. 0.5 ml of the previously prepared whole lens suspension from the contralateral eye was injected slowly under low pressure from a 22-gauge needle inserted through the wound into the mid-vitreous under ophthalmoscopic control. Finally, a sub-conjunctival injection of 20 mg gentamicin was given.

The animals were observed twice in the first week after injury, at 2 weeks after injury, and then at biweekly intervals for 6 months. The eyes were examined by slit-lamp biomicroscopy and by indirect ophthalmoscopy. Eyes with opaque media were examined by B-scan ultrasound. One of the 5 eyes was enucleated at 3 weeks after standard injury and injection of lens material. The other 4 eyes were followed up clinically for 6 months and then enucleated.

For histological examination eyes were fixed in one-half strength Karnovsky's fixative (2.5% glutaraldehyde and 2% paraformaldehyde in 0.1 M cacodylate buffer, pH 7.2) or 4% paraformaldehyde. Before enucleation 0.2 ml of fixative was injected through the pars plana away from the wound into the vitreous cavity. Immediately after enucleation a central corneal button was excised and the eyes were immersed in cold fixative for 24 hours. The eyes were then sectioned through the optic nerve and midpoint of the wound for gross examination. Each half was examined under the dissecting microscope, and drawings and photographs were made. The eyes were then dehydrated in graded alcohols, embedded in paraffin, and sectioned and stained in the routine manner. Stains used included haematoxylin-eosin, periodic acid Schiff (PAS), and Masson trichrome.

Results

CLINICAL OBSERVATIONS

The anterior chamber contained fibrin in 2 eyes for the first 2 to 3 days after injury. By 1 week the fibrin had cleared. For the duration of the follow-up period anterior segments of all 5 eyes remained free of signs of inflammation on slit-lamp examination.

The vitreous remained clear during the first week after injury and the injected lens particles were visible in the anterior and mid-vitreous. In the second week the lens particles became swollen, white, and flocculent and the surrounding vitreous mildly hazy. At 4 weeks the lens material in the vitreous was more opaque and the vitreous haze had increased so that the fundus view was obscured in all 4 eyes. The vitreous then gradually cleared, so that by 3 months the retina was again visible by indirect ophthalmoscopy. Discrete opacities of the injected lens material remained in the mid-vitreous and anterior vitreous.

Two eyes developed cataracts. In one a posterior subcapsular lens opacity was first observed at 4 months after injury, localised to the quadrant of the penetrating wound. The lens opacity progressed to involve the entire lens, which became intumescent by 6 months. In the other a localised posterior subcapsular cataract occurred but did not progress.

The penetrating wound in the pars plana was visible by indirect ophthalmoscopy. Vitreous fibrils were incarcerated in the wound, and some of the injected lens material was distributed along these vitreous fibrils. In one eye the penetrating wound healed as a flat, white scar in the pars plana. However, in the other 3 a fibrous ingrowth was apparent clinically as early as 9 weeks after injury. The ingrowth extended along the incarcerated vitreous fibrils, along the anterior hyaloid and posterior lens capsule (Fig. 1). In the eye that developed a progressive cataract the fibrous ingrowth invaded through the posterior capsule into the lens cortex.

The retina remained attached in all 5 eyes. None showed clinical signs of vitreoretinal traction or epiretinal membranes. When the fundus was not visible, a B-scan ultrasound was used to confirm that the retina remained attached.

In 1 eye at 4 months after injury small white deposits were noted along the margins of the retinal branch veins (Fig. 2a). Along the peripheral retinal veins some of these deposits became confluent, extending along and sheathing segments of the vein. The clinical appearance simulated a retinal periphlebitis, and the walls of these vessels showed some staining with dye on fundus angiography (Fig. 2b). Another eye had a similar appearance of perivascular sheathing at 3 months after injury, but

this eye developed a progressive cataract, precluding further clinical observation.

After injection the lens particles were suspended in the anterior and mid-vitreous. In 2 eyes they seemed to migrate anteriorly during the first 4 weeks after injury, but in the other 2 eyes the lens particles were distributed in a funnel-shaped con-

figuration, with the apex of the funnel attached at the optic disc. The clinical appearance and examination by B-scan ultrasound suggested the presence of a posterior vitreous detachment.

The eyes from which the lenses were extracted had an uneventful postoperative course. After the initial inflammatory reaction subsided no eyes showed signs of intraocular inflammation, and the retina remained attached in all.

HISTOLOGY

Gross examination of the enucleated eyes confirmed that the retina was attached in all eyes. One eye showed signs of minimal vitreous traction on the peripheral retina directly posterior to the penetrating wound. Fibrous ingrowth along the anterior hyaloid was present in 3 eyes and was marked in the eye in which the ingrowth invaded the lens.

Condensed vitreous fibrils were visible in the plane of the anterior hyaloid, behind the lens, and also radiating posteriorly from the penetrating wound towards the optic nervehead. Particles of the injected lens material were distributed along these vitreous fibrils.

THE WOUND

On microscopic examination good wound apposition was present in all eyes. In the eye obtained at 3 weeks after injury a round-cell infiltrate was noted in the episclera, and fibrovascular tissue was present



Fig. 1 External photograph of monkey eye focused on anterior vitreous 6 months after standard injury and injection of lens material. The anterior segment shows no signs of inflammation. Fibrous ingrowth from the area of the wound (arrow) extends across the anterior hyaloid and incorporates residual injected lens material.

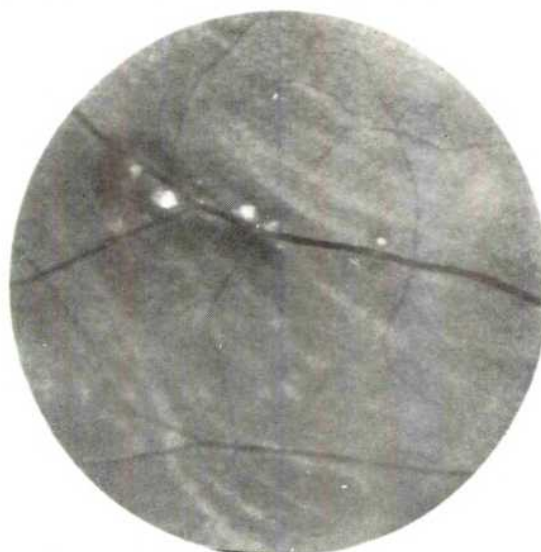


Fig. 2(a) Fundus photograph shows perivenous infiltrates in rhesus monkey eye 6 months after standard injury and injection of lens material. Infiltrates were clinically apparent along many branch veins in this eye with focal areas of sheathing in the periphery.

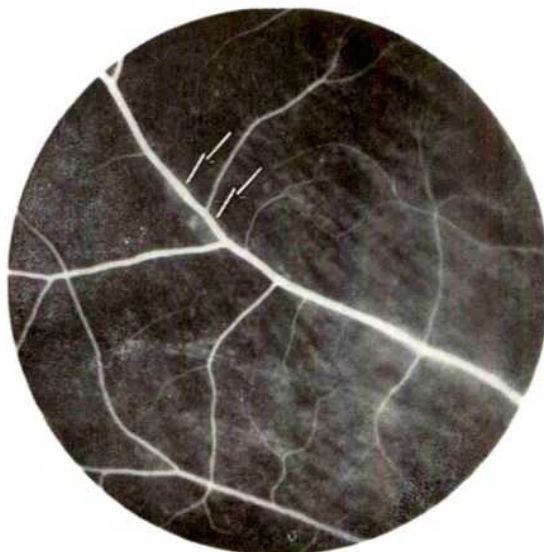


Fig. 2(b) Venous phase of fluorescein angiogram, showing same area of fundus as seen in Fig. 2(a). The vessel wall shows some staining in the area of perivascular infiltrates (arrows).

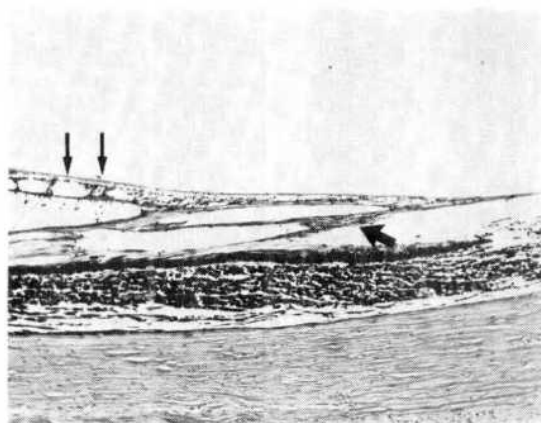


Fig. 3 Vitreous fibrils incarcerated in the wound extend posteriorly to the nonpigmented ciliary epithelium and peripheral retina. Lengthening and possibly proliferation of the nonpigmented ciliary epithelium (single arrow) has occurred. The peripheral retina is displaced anteriorly and shows cystoid degeneration, possibly due to vitreous traction (arrows). (Haematoxylin and eosin, $\times 55$).

through the full thickness of the wound and at its inner aspect. At 6 months the scleral wound appeared as a remodelled fibrous scar. Pigment granules were profusely scattered throughout the wound; some were intracellular and engulfed in phagocytic cells, but most were lying free in the mesh of the scar tissues. A few fragments of lens cortex were also present in the wound, and occasional foreign body giant cells containing refractile material were observed.

THE VITREOUS

In the eye examined 3 weeks after injury and in 1 eye at 6 months vitreous fibrils were adherent to the posterior retina. This posterior vitreous contained fragments of lens material, macrophages, and chronic inflammatory cells. In the other 3 eyes the posterior retina was entirely free of vitreous attachments.

Condensed vitreous fibrils were incarcerated in the penetrating wound and were attached to the peripheral retina and to the nonpigmented ciliary epithelium in the region of the vitreous base. Fibroblastic proliferation from the penetrating wound extended along these vitreous fibrils, anteriorly along the anterior hyaloid and posteriorly along the vitreous fibrils, and were attached to the peripheral retina and vitreous base posterior to the wound (Fig. 3).

In the eye enucleated at 3 weeks after injury the fibrous ingrowth extended as far as the equator of the lens. At 6 months 2 eyes showed a fibrous

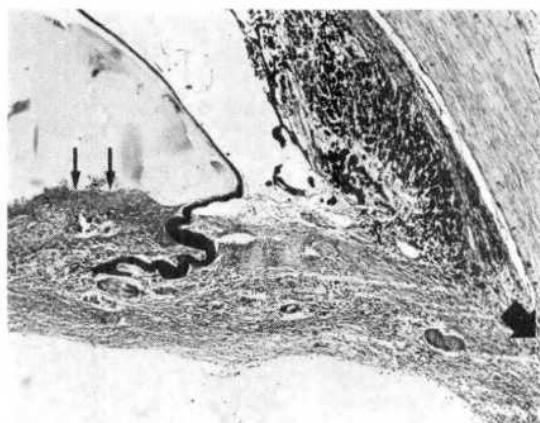


Fig. 4 Histology 6 months after injury shows marked fibrous ingrowth extending from the penetrating wound along the anterior hyaloid and posterior surface of the ciliary body (broad arrow). The fibrous ingrowth has invaded the posterior lens capsule adjacent to the wound, and there is hyperplasia of the lens epithelium (double arrow). The fibrous ingrowth contains abundant spindle cells and collagen. Scattered throughout the fibrous tissue are inflammatory cells, macrophages, and occasional foreign body giant cells. (PAS, $\times 40$).

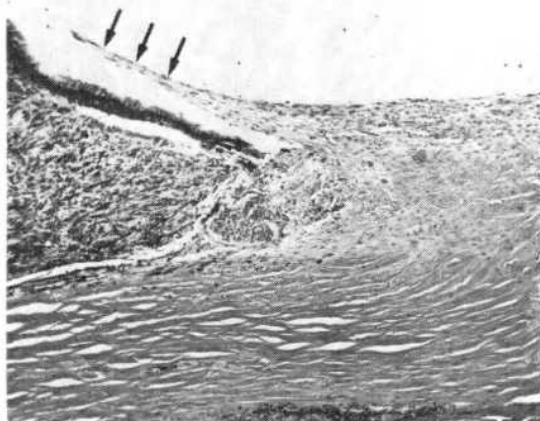


Fig. 5 At 6 months after injury and lens injection a minimal fibrous ingrowth extends from the wound along the anterior hyaloid (arrows). Note that in this case it does not reach even the ciliary processes in this section taken through its maximal extent. (Haematoxylin and eosin, $\times 60$).

ingrowth invading the lens cortex through a defect in the posterior lens capsule (Fig. 4). The fibrous ingrowth did not reach the midline in any eye and was limited to the immediate area of the wound in 1 eye (Fig. 5).

The fibroblastic proliferation within the vitreous appeared to be derived mainly from the stroma of

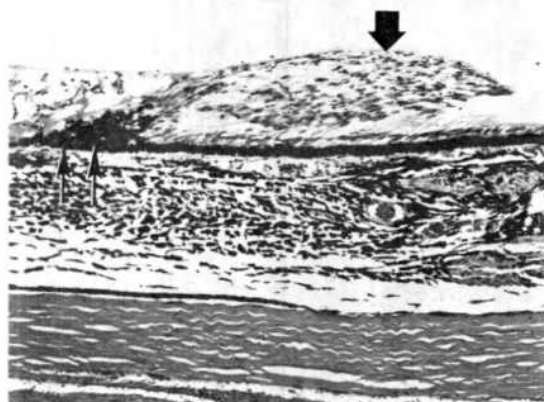


Fig. 6 Six months after injury the area immediately posterior to the wound shows proliferation of the nonpigmented (broad arrow) and pigmented (double arrows) ciliary epithelium. Cystoid degeneration of the peripheral retina is present. (Haematoxylin and eosin, $\times 80$).

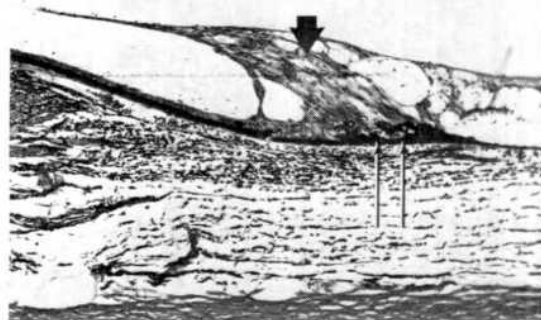


Fig. 7 Six months after injury the peripheral retina and pars plana 180 degrees away from the wound shows lengthening and probable proliferation of the nonpigmented (broad arrow) ciliary epithelium, orientated towards the attached vitreous fibrils of the anterior hyaloid. Proliferation of the pigment epithelium of the pars plana is also present (double arrows). (Haematoxylin and eosin, $\times 45$).

the ciliary body and choroid at the wound, but possibly also originated from the nonpigmented ciliary epithelial cells posterior to the wound, became greatly elongated in the direction of the vitreous fibrils that were incarcerated in the wound and were attached to these cells (Fig. 6). In 1 eye a mound of cells proliferated at the junction of the ora serrata and pars plana 180° from the penetrating wound (Fig. 7). Most of these proliferating cells had rounded nuclei and abundant clear cytoplasm, but there were several layers of pigment-containing cells at the base of the mound (Figs. 6 and 7). The appearance suggested the possibility of proliferation of both the pigmented as well as the nonpigmented ciliary epithelium.

The fibrous ingrowth contained a few fine capillaries, chronic inflammatory cells, and pigment-containing macrophages. Occasional multinucleated giant cells were present surrounding or engulfing small refractile particles. Remnants of injected lens capsule were also visible. In 2 eyes where the fibrous ingrowth invaded the lens capsule proliferation of the lens epithelium may have contributed to the fibrous ingrowth (Fig. 4).

RETINA

In the 4 eyes with a fibrous ingrowth from the wound the peripheral retina posterior to the wound showed a characteristic appearance. This peripheral retina was drawn anteriorly towards the pars plana. Vitreous fibrils radiated between this peripheral retina and the penetrating wound, suggesting the presence of vitreous traction. To a variable extent

the pulled-forward peripheral retina showed cystoid degeneration, and a small localised retinal detachment was present in 1 eye (Fig. 3). Also in 1 eye this same appearance of vitreous traction on the peripheral retina was visible at 180° from the penetrating wound (Fig. 7). None of these eyes showed any evidence of epiretinal membranes, despite extensive sectioning.

Macrophages were occasionally present in the inner retina. A few macrophages and particles of injected lens material were usually found scattered along the internal limiting membrane over the peripheral and posterior retina and at the optic nerve head.

In the eye with clinical signs of retinal periphlebitis light microscopy showed cuffing of the retinal veins with inflammatory cells, mostly lymphocytes, but also eosinophils and occasional macrophages (Fig. 8). In the eye enucleated at 3 weeks after injury a precisely similar appearance was found. In addition the retinal blood vessels, both arteries and veins, at the optic nerve head showed perivascular infiltrates composed of lymphocytes and plasma cells in 4 of 5 eyes (Fig. 9). Three of these eyes also showed evidence of a limited fibroglial proliferation at the optic nerve head. The iris and ciliary body were found to contain focal round cell infiltrates in some sections. The choroid showed no histological evidence of inflammation in any of the eyes studied.

The eyes from which lenses were extracted had no evidence of inflammation in the iris, in the ciliary body, or in the choroid. The retinal blood vessels contained no perivascular infiltrates. The optic

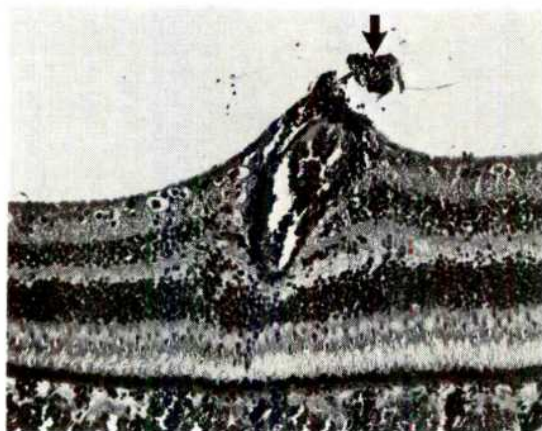


Fig. 8 Histological appearance of perivascular infiltrates shown in Figs. 2(a) and 2(b). Lymphocytes, plasma cells, eosinophils, and occasional macrophages surround the wall of retinal vein. Vitreous fibrils are adherent to the surface of the retina overlying the blood vessel. In processing, a segment of the infiltrate has become separated (arrow). (Haematoxylin and eosin, $\times 100$).

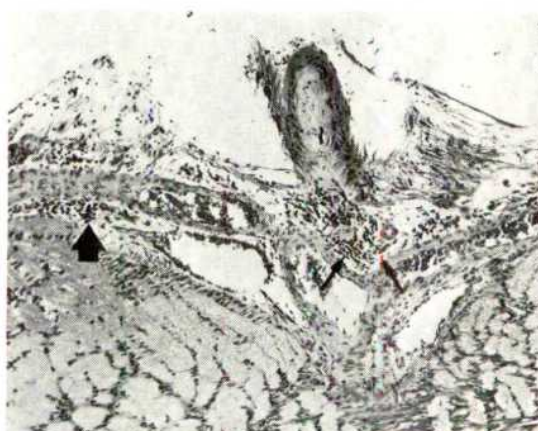


Fig. 9 Six months after injury fibroglial proliferation at the optic nervehead is present. A blood vessel sectioned longitudinally at the optic nervehead (broad arrow) shows a perivascular cuff of lymphocytes and plasma cells. Smaller blood vessels in the nerve head (double arrows) also show perivascular infiltrates. (Haematoxylin and eosin, $\times 78$).

nerve head was free of inflammatory cells or fibroglial proliferation. In these eyes the retina was attached without signs of vitreous traction.

Discussion

Clinical studies of penetrating eye injuries have identified vitreous lens admixture as a potent stimulus of intravitreal fibroblastic proliferation and thus as an indication for early vitrectomy.^{10 15 18 21} Moreover, clinical impressions are reinforced by the histopathology of enucleated specimens that indicate the injured lens may contribute to vitreous organisation, either as an inflammatory stimulus or as a source of cellular proliferation.¹⁵ However, the precise role of the lens in promoting intravitreal fibrocellular proliferation remains difficult to define in clinical situations, because lens injury is so often accompanied by damage to other ocular tissues or vitreous haemorrhage, which may constitute equal or greater stimuli to intraocular cellular proliferation.

It is acknowledged that intravitreal lens fragments after cataract surgery may result in persistent uveitis with vitreous opacification and condensation.^{25 26} Such a reaction may result in fibrocellular proliferation within the vitreous and may culminate in traction retinal detachment. The lens has been similarly implicated in the intraocular inflammation occurring in phacoanaphylaxis, sympathetic ophthalmia, and chronic nongranulomatous, lens-induced uveitis.^{27 28} However, as with penetrating

injuries, these clinical situations are often accompanied by other complications, such as uveal or vitreous prolapse, obscuring the exact role of the lens in the pathogenesis of the ocular response.

A previous report detailed studies which combined a standard posterior penetrating injury with injection of autologous whole blood to simulate vitreous haemorrhage.²² Massive cellular proliferation occurred within the vitreous and resulted in nonrhegmatogenous traction retinal detachment in 80% of injured eyes. An identical wound with injection of an equal volume of balanced salt solution caused little vitreous reaction and no retinal detachment.

In this study, when the standard injury was combined with an intravitreal injection of autologous emulsified whole lens, the response within the vitreous was much more limited than in eyes with blood injection.^{22 23} A fibrous ingrowth was present containing spindle cells and abundant collagen and originating mainly from the wound. It also contained moderate numbers of chronic inflammatory cells, macrophages, and foreign body giant cells. In 2 eyes where the posterior capsule of the in-situ lens proved to be ruptured on histological section, the lens epithelium appeared to be hyperplastic and may have contributed to the fibrous ingrowth. It was unlikely that such proliferation was due to rupture of the lens at the time of injury, since all injections were performed under ophthalmoscopic control with the needle tip continuously visible. Moreover, in the earlier series of saline- and blood-

injected eyes, by the same surgeon using identical techniques, similar proliferations of the lens epithelium were not observed, nor was there any inadvertent perforation of the lens. It is tempting to speculate that the injected lens material may have stimulated secondary changes in the in-situ lens.

The extent of the fibrous ingrowth varied from essentially absent to moderate among the eyes in this series. It was most prominent at the inner aspect of the wound and extended along the scaffold of the anterior hyaloid and to a less extent posteriorly along the vitreous base, much as in blood-injected eyes.²³ The most prominent fibrous ingrowth occurred in eyes with rupture of the posterior capsule of the in-situ lens.

It is impossible to determine whether the greater fibrous ingrowth contributed to lens rupture or the reverse situation occurred. One might speculate that either rupture of the lens incited greater vitreous reaction or vitreous inflammation resulted in cataract and lens rupture. The observation of either indicates the need for a further series of animal experiments with rupture of the in-situ lens.

Periretinal membranes were not observed clinically or histologically in this series, unlike previous blood-injected eyes.²³ Although the stimuli to formation of epiretinal membranes are uncertain, it is generally predicated that the integrity of the retina must be breached by mechanisms such as inflammation, retinal tear, or posterior vitreous detachment for proliferation of glial or pigment epithelial elements to occur.^{29,30} In our previous studies of injury with blood injection epiretinal membranes consisting of glial and fibrous elements were observed on the peripheral and posterior retina.²³ A prominent mononuclear response in these eyes occurred, and electron micrographs showed macrophages traversing the internal limiting membrane, possibly leaving defects through which glial elements could gain access to the surface of the retina.³¹ Humoral factors elaborated by the intense macrophage response may also have stimulated fibroglial proliferation, both in the vitreous and on the retina. Lens-injected eyes contained considerably fewer macrophages on histological section than blood-injected eyes. Also, posterior vitreous detachment occurred almost universally in blood-injected eyes but in only 2 of the lens-injected eyes, eliminating another possible stimulus to epiretinal membrane formation.

No clinically evident traction retinal detachments occurred in the present series of eyes, though microscopic evidence of vitreoretinal traction occurred posterior to the wound and at the peripheral retina 180° away. The absence of retinal detachment can be attributed to limited fibrous ingrowth from

the wound and to the absence of periretinal membranes, which in earlier experiments combined to exert traction on the vitreous base and circumferential retinal traction.

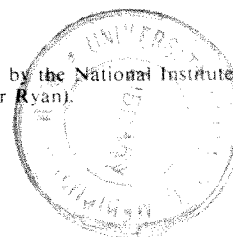
The inflammatory response observed after injury and lens injection were limited to focal round-cell infiltration of the iris, ciliary body, optic nerve head, and a retinal perivasculitis. Scattered macrophages and foreign body giant cells were observed in the wound and fibrous ingrowth. These giant cells and a portion of the inflammatory exudate in the vitreous may have been a response to the refractile material observed in microscopic sections of the wound, fibrous ingrowth, and vitreous. These particles were not observed in the histology of previous series and were probably fragments of the mortar and pestle used to emulsify an injected lens.

Reactions resembling phacoanaphylaxis, sympathetic ophthalmia, or other lens-induced uveitis were not observed in this series. In fact the overall inflammatory response was less marked than would have been expected based on clinical studies of penetrating injuries with lens damage. It is recognised that penetrating injuries without lens damage may cause uveal and retinal inflammation similar to that observed in this series,³² and, moreover, the histology of animals with a standard wound and blood injection also showed a perivasculitis and uveitis.³³ It is possible, however, in the lens-injected eyes that the inflammatory signs observed were the residua of an earlier, more prominent reaction.

Before concluding that vitreous-lens admixture may not be as serious as previously thought it must be realised that animal models of lens-induced uveitis have been difficult to produce.^{24,34,35} It is possible that species variability and the lack of presensitisation to lens protein may account for the lesser reaction. The uninjured in-situ lens and intact anterior vitreous face of our model are not analogous to most penetrating injuries with lens damage and may play a role in the minimal ocular response observed. Therefore further experiments with greater numbers and damage to the in-situ lens are indicated.

These experiments indicate that in the rhesus monkey eye vitreous-lens admixture is a much less potent stimulus to intravitreal fibroblastic proliferation and to traction retinal detachment than vitreous haemorrhage. The study reinforces our impression that periretinal membranes are a very important factor in inducing traction retinal detachment.

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Penetrating eye injuries: a histopathological review

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SUMMARY This study reports the histological findings in human eyes after severe penetrating trauma. The findings confirm the high incidence of retinal detachment in eyes with severe penetrating injuries. The retina was detached in 32 out of the 34 eyes examined, with 27 having evidence of traction on the retina. These eyes were characterised histologically by intraocular cellular proliferation producing cyclitic, epiretinal, and retrolental membranes. Intraocular cellular proliferation was discernible or established within 1 week of injury and typically resulted in a cyclitic membrane at about 6 weeks. Epiretinal and retrolental membranes were found between 1 and 2 weeks after injury in eyes with a detached retina. The results indicate that a damaged lens, the admixture of lens material and vitreous, and the presence of vitreous haemorrhage were all factors promoting intravitreal fibroblastic proliferation. Vitreous surgery may be a rational method of treatment for these severely injured eyes by removing the stimulus and vitreous scaffold for intravitreal fibroblastic proliferation. From this series it would appear that vitrectomy should not be delayed beyond the second week of injury, by which time massive cellular ingrowth may already be under way.

Ocular trauma is an important cause of blindness,¹ and in some centres it accounts for half or more of all eyes enucleated.² Among eye disorders ocular trauma is responsible for a disproportionate economic problem, as it occurs most commonly in young, otherwise healthy, productive individuals.³ Penetrating injuries of or involving the posterior segment of the eye have a particularly poor visual prognosis because of the high incidence of retinal detachment,⁴⁻⁷ whereas in penetrating injuries confined to the anterior segment of the eye a relatively better visual outcome can be expected.⁸ Improved results for anterior segment injuries can be attributed to the introduction of microsurgical techniques, antibiotics, and steroids.⁹ Recent experience with new surgical techniques such as vitrectomy suggests that it is now also possible to salvage some eyes with severe posterior segment injuries.¹⁰⁻¹³

This study reports the histological findings in human eyes enucleated after severe penetrating trauma and correlates the occurrence and chronology of various tissue reactions with time after injury. It was of special interest to characterise early changes occurring after injury and to deter-

mine how they might trigger the mechanisms responsible for eventual retinal detachment. Knowledge of the chronology of histopathological events after severe penetrating trauma may help determine a rationale for surgical management of these cases and specifically identify the optimal timing for surgical intervention by pars plana vitrectomy.

Material and methods

We reviewed case reports from 1970 to 1977 in the pathology files of the Estelle Doheny Eye Foundation and retrieved slides on 72 cases with a diagnosis of ruptured globe or penetrating eye injury. Among these were 34 eyes enucleated between 1 day and 3 years after the original injury which could be analysed histologically with reference to: (1) the status of the wound; (2) the presence of damage to the uvea, the lens, the vitreous, or the retina; (3) intraocular cellular proliferation; (4) intraocular inflammation.

Multiple sections were examined from each case stained with haematoxylin-eosin, periodic acid Schiff (PAS), Masson-trichrome, alcian blue with and without digestion by hyaluronidase, and the Prussian blue reaction for iron.

The remaining 38 eyes were either enucleated

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soon after injury or were too disorganised to permit accurate evaluation of individual histological features. They were excluded from the study.

Results (Table 1)

THE WOUND

The site of penetration was limited to the cornea in 16 eyes, included the peripheral cornea and adjacent sclera in 13 eyes, and involved the sclera alone in 5. The full extent of the penetrating wound was determined by compiling information from clinical and operative reports, gross histological descriptions, and light microscopy.

Corneal wounds were closed externally by sliding and hyperplasia of epithelial cells within 1 week of injury. A fibrous stromal scar was present by 3 to 4 weeks in those wounds with good closure where no uveal or vitreous incarceration had occurred. Delayed healing of corneal wounds was common and could be related to defective wound closure, especially with incarceration of intraocular tissues in the wound. We judged wound apposition as particularly poor in 12 eyes, 9 of which had to be enucleated within 2 weeks of injury. Poor wound closure varied from a wide gap to moderate malapposition of the wound edges. Many corneal wounds showed posterior wound gape, probably related to superficial placement of sutures.

Healing of limbal and scleral wounds was more rapid than in corneal wounds. As early as 4 days after injury fibroblastic proliferation had occurred from the episclera, and by 1 week it occurred from the stroma of the ciliary body and choroid. At 2 weeks a mass of vascularised fibrous tissue joined the wound edges, and by 4 to 6 weeks a dense

fibrous scar had formed. Pigment, both free and within macrophages, was scattered throughout the scar tissues.

Of the 34 eyes 28 showed prolapsed or incarcerated tissues in the wound, including lens material, lens capsule and retina, and most commonly uvea or vitreous. Incarceration of tissues in a corneal wound was consistently associated with a delay in wound healing in eyes enucleated within the first 2 weeks of injury, and with the development of fibrous ingrowth from the wound in eyes enucleated from 3 weeks onward. Incarceration of tissues in limbal or scleral wounds was associated with the formation of granulation tissue in the wound, often extending intraocularly into the adjacent incarcerated tissue.

A single eye with poor closure of a corneal wound showed an epithelial ingrowth. Fibrous ingrowth from the wound occurred in 19 of the 34 eyes. It did not occur from corneal wounds without incarceration of tissues in the wound, or at least apposition of tissues to the wound, such as a damaged lens or iris. In limbal or scleral wounds fibrous ingrowth occurred despite good wound closure. These eyes, however, often had obvious vitreous incarceration in the wound, and they usually showed damage to the lens and/or vitreous haemorrhage.

THE VITREOUS

Early changes in the structure of the vitreous gel after injury included separation of the vitreous from the posterior retina and condensation of vitreous fibrils over the vitreous base. The vitreous had separated from the posterior retina in six of the 13 eyes examined between 1 and 2 weeks after injury. Of a total of 22 eyes with a posterior vitreous detachment 18 had blood loculated in the vitreous gel. In the early weeks after injury, the surface of the posterior hyaloid consisted of a discrete layer of condensed vitreous lined by red blood cells and macrophages, and in 1 eye at 2 months after injury it also contained fibroblast-like cells.

The vitreous did not become detached anteriorly. Typically, condensed vitreous fibrils remained attached to the peripheral retina and nonpigmented ciliary epithelium over the vitreous base. Vitreous fibrils often radiated from a limbal or scleral wound in which they were incarcerated, and fibroblasts were typically aligned along these fibrils. In some eyes the vitreous fibrils appeared taut and seemed to account for traction detachment of the peripheral retina 180° from a penetrating limbal or pars plana wound (Fig. 1).

Condensed vitreous fibrils were also prominent in eyes with double perforating injuries due to a foreign body. These fibrils were incarcerated in the entry and exit wound, bridging the vitreous cavity.

Table 1 *Time at which eyes were examined after injury*

<i>Time after injury</i>	<i>Eyes examined</i>
1 day	2
7 days	5
12 "	3
14 "	5
3 weeks	1
4 "	1
6 "	3
2 months	5
4 "	2
5 "	1
6 "	3
18 "	1
2 years	1
3 "	1

INTRAOCULAR INFLAMMATION

Intraocular inflammatory infiltrate was quite variable, but was often prominent in the anterior chamber or vitreous, especially in the presence of blood. Inflammatory cells, usually mainly monocytes, often surrounded the site of rupture of the lens capsule or were present in the penetrating wound or in the incarcerated tissues. The inflammatory response was most marked in eyes with lens, vitreous, and blood admixture. Macrophages were present in these eyes, surrounding lens fragments or at the margins of blood clot within the vitreous. Almost all eyes contained some macrophages either lining the posterior vitreous separation or accumulated in areas of subretinal haemorrhage.

INTRAOCULAR CELLULAR PROLIFERATION

Fibroblastic proliferation within the vitreous was

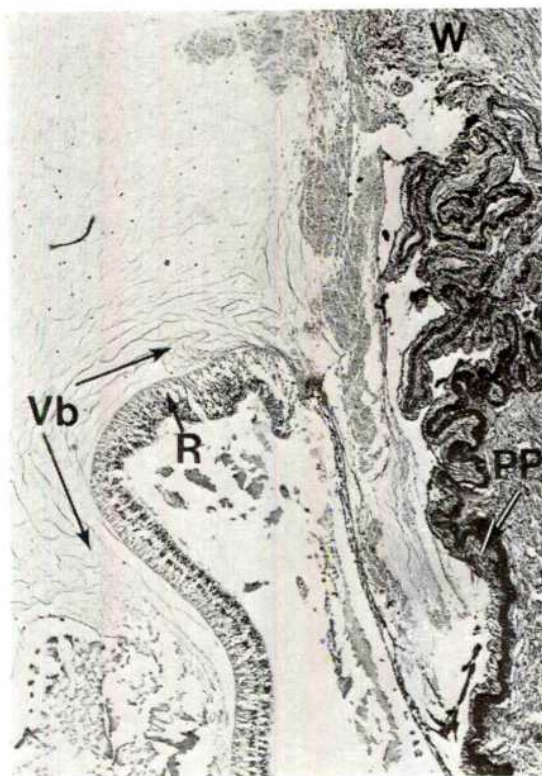


Fig. 1 Photomicrograph showing the appearance of the peripheral retina in the vitreous base at 2 months after a penetrating injury. The peripheral retina (R) is detached and appears to be pulled forward over the pars plana (PP). The vitreous is condensed and vitreous fibrils are incarcerated in a peripheral corneal wound (W). The vitreous was detached from the posterior retina, but remains attached to the peripheral retina over the vitreous base (VB). (Haematoxylin and eosin, $\times 37$).

present as early as 1 week after injury and most often emanated from the stroma of the ciliary body or choroid at a limbal or scleral wound. The invading fibroblasts appeared to extend along the scaffold provided by vitreous fibrils or into the blood clot and the vitreous gel behind the lens (Fig. 2). Fibroblastic proliferation also extended posteriorly over the pars plana and on to the surface of the peripheral retina. Fibrous proliferation within the vitreous resulted in a cyclitic membrane in which lens material, lens capsule, and detached retina were often incorporated. We found cyclitic membranes in 17 eyes as early as 2 weeks after injury in 2 eyes that had a limbal wound and vitreous haemorrhage and prolapse of the lens. The cyclitic membrane was well established in most eyes by 6 to 8 weeks after injury.

Cellular proliferation within the vitreous also appeared to originate from the nonpigmented ciliary epithelium. Characteristically these cells became elongated and at 1 week after injury appeared to be proliferating into the vitreous cavity along the vitreous fibrils attached over the vitreous base (Fig. 2).

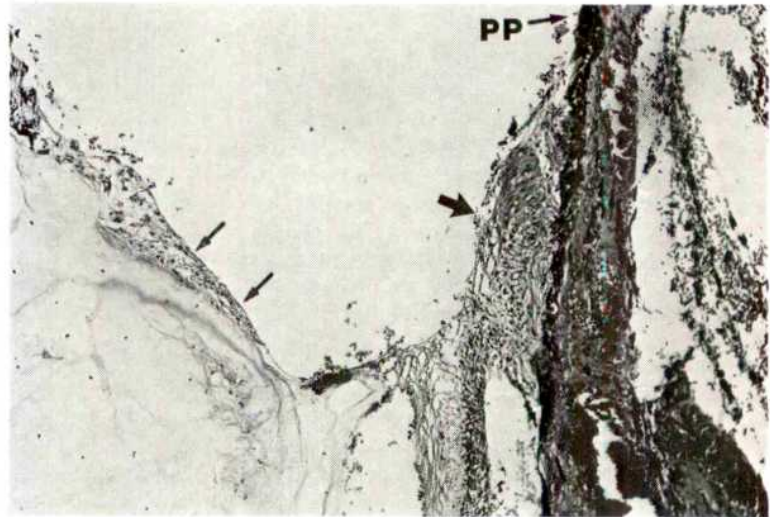
Intravitreal fibroblastic proliferation also appeared to occur from the exit wound in eyes with double perforating injuries.

THE RETINA

Retinal detachment was present in 32 out of 34 eyes. The 2 eyes without a retinal detachment had been enucleated as blind and painful because of uncontrolled glaucoma. We found retinal tears in only 2 eyes, but it was impossible to exclude a rhegmatogenous component in the others as we did not serially section all eyes. Retinal haemorrhages were present in all 20 eyes enucleated within the first 2 months of injury. Choroidal haemorrhages were also common within the first 2 to 3 weeks after injury, and ciliary body effusions were frequent in eyes with cyclitic membranes.

Epi-retinal membranes were present in 14 eyes. They seemed to originate from the fibrous ingrowth from the wound, or from the surface of the optic nerve head, or from the surface of the retina. Epi-retinal membranes were present over the peripheral retina in 2 eyes examined at 2 weeks after injury and consisted of spindle cells which seemed to have their origin in the fibrous ingrowth from an adjacent penetrating wound through the limbus or pars plana (Fig. 3). Similarly, by 12 days after injury spindle cells had formed an epi-retinal membrane over the posterior retina adjacent to an exit wound in an eye with a double perforating injury (Fig. 4). By 4 to 6 weeks after injury multilayered epi-retinal membranes could be found over both peripheral (Fig. 5) and posterior retina (Fig. 6).

Fig. 2 Photomicrograph demonstrating the peripheral retina and pars plana (PP) 180° from a penetrating wound through the pars plana in an eye enucleated 1 week after injury. There is an apparent proliferation of the nonpigmented ciliary epithelium (large arrow). Cellular proliferation has also occurred along the anterior hyaloid (small arrows). Possibly these cells are derived from the nonpigmented ciliary epithelium. (Haematoxylin and eosin, $\times 64$).

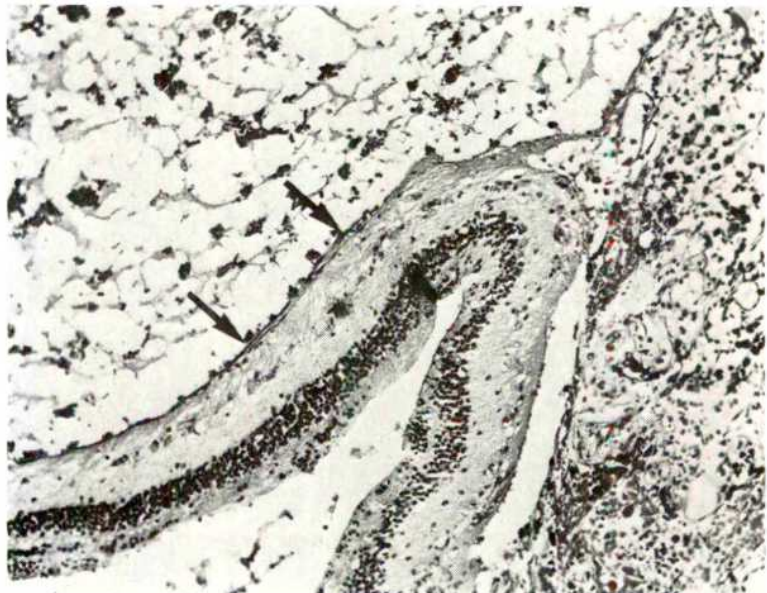


These membranes also contained pigmented cells and macrophages and some had connections to the surface of the retina. In 10 of 16 eyes the epiretinal membranes were also connected to the surface of the optic nerve head. Thick multilayered epiretinal membranes were often associated with full-thickness retinal folds.

We found retroretinal membranes in 15 eyes. They were present in 6 of 13 eyes examined between 1 and 2 weeks after injury. In the early cases the membranes were delicate, branching, and dendritic in appearance. In late cases they were thickened

and attached to folds in the retina. The pathogenesis of the retroretinal membranes was not clear, but they were often found in areas of subretinal haemorrhage (Fig. 7). In 1 eye at 1 week after injury a small retroretinal membrane composed of nonpigmented cells was connected to and extended along the outer retina (Fig. 8). In eyes examined at 2 weeks after injury prominent retroretinal membranes were present and appeared continuous with areas of proliferation of the retinal pigment epithelium. At 2 weeks also, in eyes with choroidal and subretinal haemorrhage, cellular invasion of the subretinal

Fig. 3 Photomicrograph showing the appearance of the peripheral retina posterior to a penetrating wound through the pars plana in an eye enucleated 2 weeks after injury. The peripheral retina appears to be pulled forward over the pars plana. Spindle cells are present on the surface of the peripheral retina (arrows) and have probably originated from the wound or from proliferation of the ciliary epithelium posterior to the wound. (Haematoxylin and eosin, $\times 86$).



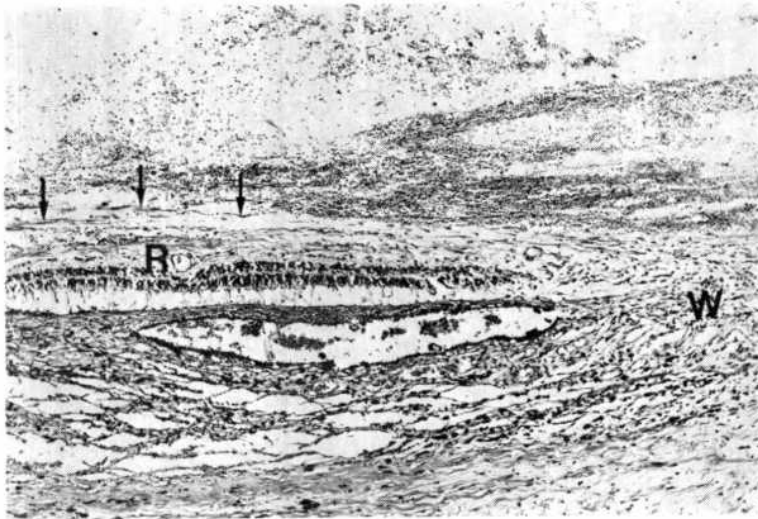


Fig. 4 Photomicrograph showing the appearance of a posterior penetrating wound at 12 days after injury in an eye with a double perforating injury due to an intraocular foreign body. Spindle cells (arrows) are emanating from the wound (W) on to the surface of the peripheral retina (R), and appear to be infiltrating the vitreous and blood clot. These spindle cells may originate from the choroid, or possibly have their origin in metaplastic retinal pigment epithelial cells or in the episclera. (Haematoxylin and eosin, $\times 43$).

blood clot occurred, apparently from the choroid through breaks in Bruch's membrane (Fig. 9).

Discussion

We analysed the histological findings in 34 eyes enucleated after penetrating trauma. These eyes were characterised histologically by intraocular cellular proliferation leading to the formation of cyclitic, epiretinal, and retroretinal membranes and by the presence of traction retinal detachment. These findings support clinical studies in which traction retinal detachment has been identified as a main cause of loss of vision after a posterior penetrating injury.⁴⁻⁷

Immediately after injury an expulsive type of haemorrhage may occur with bleeding into the choroid, under the retina, and into the vitreous. If the expulsive haemorrhage results in prolapse of the intraocular contents, there is little potential for visual recovery.⁷ In the injured eye an inflammatory response occurs, the extent of which is influenced by various factors, such as vitreous haemorrhage, vitreous-lens admixture, or the presence of a reactive intraocular foreign body or of infection. As the inflammation subsides, cellular invasion and proliferation within the vitreous occur. Physical alterations in the structure of the vitreous may provide a more effective scaffold for intravitreal cellular proliferation.¹¹ The proliferating cells give rise to

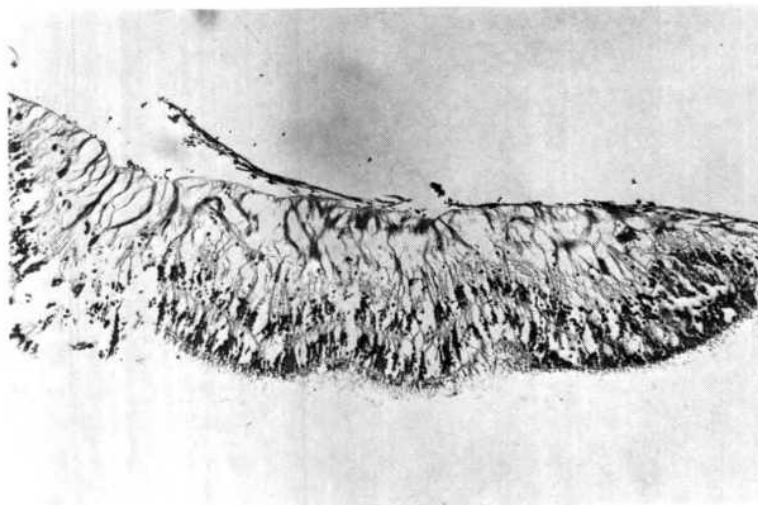
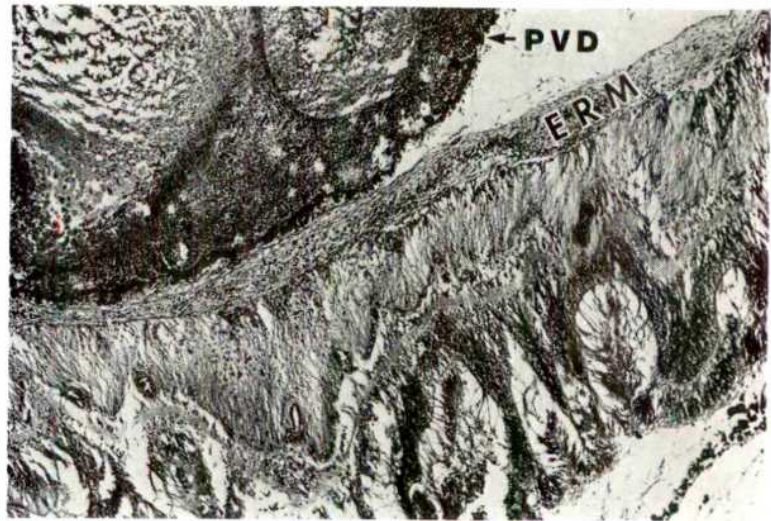


Fig. 5 Photomicrograph of peripheral retina from an eye with a total retinal detachment enucleated 6 weeks after a penetrating injury shows an epiretinal membrane 3 layers thick present on the surface of the retina. The epiretinal membrane is artefactually detached, revealing an apparently intact inner limiting membrane. (Haematoxylin and eosin, $\times 68$).

Fig. 6 Photomicrograph showing a multilayered epiretinal membrane (ERM) on the surface of the posterior retina in an eye enucleated 2 months after a penetrating injury. A posterior vitreous detachment (PVD) is present and blood clot is loculated within the vitreous gel. The posterior hyaloid (PVD) is lined with red cell debris. The epiretinal membrane lies between the posterior hyaloid and the inner limiting membrane of the retina. In adjacent sections full-thickness retina folds were present. (Haematoxylin and eosin, $\times 37$).



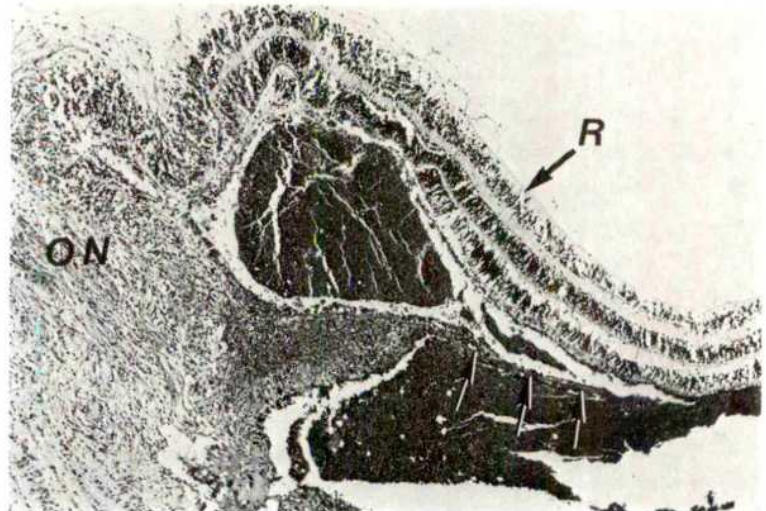
cyclitic or transvitreal membranes and to epiretinal and retrolental membranes. Ultimately cells within these membranes contract, producing traction on the retina and resulting in traction retinal detachment.¹⁴

In this study intraocular cellular proliferation was discernible or established within 1 week of injury and typically resulted in a cyclitic membrane at about 6 weeks. A cyclitic membrane was present as early as 2 weeks after injury in eyes with limbal or scleral wounds associated with incarceration of lens material, vitreous, and blood. The factors associated with a vigorous fibrous ingrowth and intra-vitreal fibroblastic proliferation were the site of the penetrating wound; the adequacy of wound closure; the incarceration of tissues in the wound;

the extent of involvement of intraocular tissues including the iris, lens, and vitreous; and the presence of massive vitreous haemorrhage.

Cellular proliferation within the vitreous appeared to be derived from multiple sources, usually from the episclera and from the uvea in the area of a perforating scleral or limbal wound. Proliferation of the nonpigmented ciliary epithelium was also a common finding. These cells became elongated and extended along the vitreous fibrils into the vitreous cavity, apparently contributing to the formation of cyclitic membranes. Hyperplasia of the nonpigmented ciliary epithelium has been observed by others in a variety of conditions, including trauma and inflammation.^{2,15} It is also possible that the

Fig. 7 Photomicrograph showing the appearance of the posterior retina (R) and optic nerve head (ON) in an eye enucleated 12 days after a penetrating injury. A subretinal haemorrhage is present, and spindle cells have formed a retrolental membrane (arrows) in the blood clot. Possible origins of this membrane would include adjacent pigment epithelial cells, or glial cells from the retina, or from the glial lining of the optic nerve. (Haematoxylin and eosin, $\times 43$).



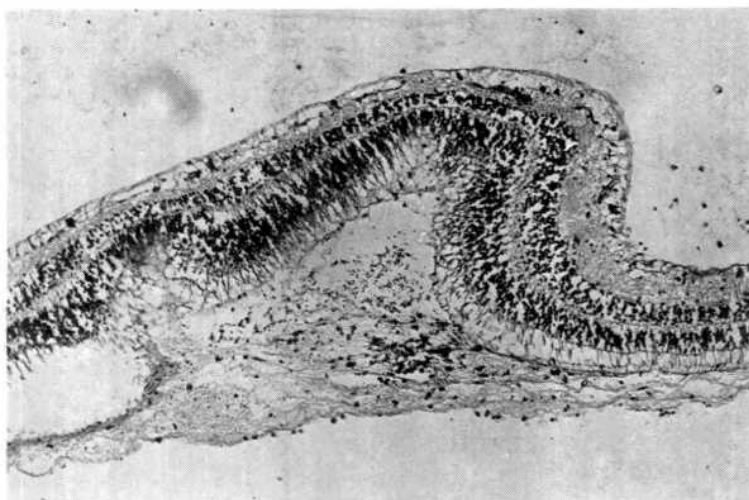


Fig. 8 Appearance of a retroretinal membrane under the equatorial retina 1 week after a penetrating injury. (Haematoxylin and eosin, $\times 77$).

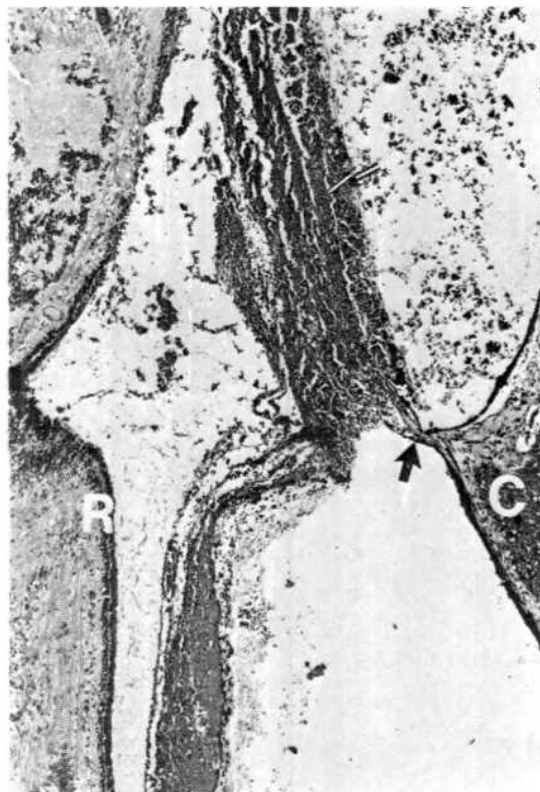


Fig. 9 Photomicrograph showing the subretinal space in an eye enucleated at 2 weeks after penetrating injury. A subretinal blood clot (BC) is present, and fibroblasts are invading the blood clot and subretinal space through a break in Bruch's membrane (arrow). The retina (R) is detached and partially necrotic. Bleeding has also occurred in the choroid (C). (Haematoxylin and eosin, $\times 42$).

intravitreal fibroblastic response may have been derived in part from macrophages or monocytes originating in the systemic circulation, though most of the experimental evidence now supports the view that fibroblasts involved in wound healing are derived locally.^{16,17}

Intraocular cellular proliferation also included the formation of epiretinal and retroretinal membranes which were prominent between 1 and 2 weeks after injury. The epiretinal membranes over the peripheral retina and over the posterior retina adjacent to exit wounds in eyes with double perforations appeared to be derived from fibroblastic ingrowth from the area of the penetrating wound. A similar appearance has been observed in experimental animal models of a posterior penetrating eye injury.¹⁸⁻²⁰ On the other hand some epiretinal membranes were connected to the surface of the retina by bridges of tissue suggesting a glial component, a feature which has also been described in experimental animal models.^{14,20} The retroretinal membrane probably originated from glial cells in the retina or from proliferation of retinal pigment epithelial cells. Additionally, in some eyes with choroidal and subretinal haemorrhage, fibroblasts proliferated from the choroid through breaks in Bruch's membrane into the subretinal space.

The concept that damaged vitreous forms a scaffold or matrix for cellular proliferation was supported by this study. We observed a condensation of the anterior vitreous fibrils in virtually all cases. When vitreous was incarcerated in a penetrating wound, vitreous strands formed between the wound and the peripheral retina over the vitreous base, and in those eyes with a double perforating injury the vitreous fibrils were aligned between

entry and exit wounds. Ingrowing fibroblasts along these vitreous condensations suggest that the vitreous acts as a scaffold for the directed proliferation of cells. In a similar fashion fibroblasts from the penetrating wound proliferated along the surface of the retina. These findings are in accord with information derived from growth of fibroblasts in tissue culture, where it has been observed that cells use linear structures and scaffolds for directed proliferation.¹⁷

We found evidence of traction on the retina in 27 eyes, either by epiretinal or retrolental membranes or signs suggesting vitreoretinal traction. Retinal tears were observed histologically in only 2 eyes, but it was impossible to exclude a rhegmatogenous component in the others, and certainly a severe penetrating injury may result in retinal dialysis or a retinal tear as part of the contusive effect. Nevertheless the characteristic configuration of the detached peripheral retina pulled anteriorly over the pars plana and the presence of retinal folds related to epiretinal and retrolental membranes suggested that traction mechanisms were important in the evolution of eventual total retinal detachment. We observed a similar appearance in an experimental animal model of a posterior penetrating eye injury and proposed that the mechanisms for traction retinal detachment after a penetrating injury are due to the effects of vitreous traction on the peripheral retina over the vitreous base and contraction of epiretinal and retrolental membranes on the peripheral and equatorial retina.^{14 20 21} We have also noted in this study and in experimental models that with a double perforating injury anteroposterior vitreous traction may be observed.^{18 22} But, typically, in single perforating wounds through the limbus or pars plana the vitreous detaches from the posterior retina without any subsequent anteroposterior traction.

In this study fibrous ingrowth occurred from corneal wounds only with poor wound closure and with incarceration of tissues in the wound. Conversely, with limbal or scleral wounds a fibrous ingrowth was common despite good wound closure, but usually associated with damage to the lens and/or vitreous haemorrhage. Development of fibrous ingrowth from scleral wounds despite good wound closure is in accordance with findings from experimental animal models of posterior penetrating eye injuries which emphasised the prognostic significance of blood in the vitreous and damage to intraocular structures in severe penetrating trauma.^{18 20}

The clinical implications of this study are numerous. It is clear that the primary surgical repair of penetrating wounds must include thorough explora-

tion and debridement with microscopic reapproximation of wound edges. Prolapsed or incarcerated tissue must be excised or repositioned. Vitreous incarceration in a corneal wound can be avoided, but it is probably impossible to avoid incarceration of vitreous in scleral wounds.

The results of this study indicate that, with a posterior penetrating eye injury and in the presence of retinal detachment, significant cellular proliferation is present within the vitreous and along the surfaces of the retina as early as 2 weeks after injury. The results also indicate that a damaged lens, the admixture of lens material and vitreous, and the presence of a vitreous haemorrhage are all factors promoting intravitreal fibroblastic proliferation. It has not been possible in this study or in others to determine the significance of each one of these factors in stimulating the intravitreal fibroblastic response.⁹ Vitreous surgery may be a rational method of treatment for these eyes by removing the stimulus and vitreous scaffold for intravitreal fibroblastic proliferation. From this series of post-trauma human eyes it would appear that vitrectomy should not be delayed beyond the second week of injury, by which time massive cellular ingrowth may already be under way.

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Experimental occlusion of the central artery of the retina. IV: Retinal tolerance time to acute ischaemia*

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SUMMARY Ophthalmoscopic, fluorescein angiographic, electrophysiological, and morphological studies on 63 eyes of rhesus monkeys with acute transient experimental occlusion of the central artery of the retina (OCAR) showed that the retina suffered irreparable damage after ischaemia of 105 minutes but recovered well after ischaemia of 97–98 minutes. The tolerance time of the brain to acute transient ischaemia is many times shorter than that of the retina. The metabolism of ischaemic neurones (in the retina and brain) is discussed with a view to explaining this difference, and also the various factors possibly responsible for the retina's longer tolerance of ischaemia, as compared to the brain.

Occlusion of the central artery of the retina (OCAR) is a true ophthalmic emergency, when every minute that elapses increases the chances of death of the retina. It is therefore absolutely essential to know how long it takes for acute retinal ischaemia to produce irreversible damage. Much of the confusion about this length of time is due to the many conflicting claims reported in anecdotal clinical case studies and in animal experiments, so that it is not at all surprising that in spite of the considerable interest which this subject has attracted no definite conclusion has been reached so far.

Previous studies

CLINICAL CASE REPORTS

Table 1 comprises most of the available reports in the English literature plus a few from other languages. Recovery of retinal function is said to take place after an ischaemia of anything from 10 minutes to as much as 36 hours. In addition there are 2 more reports in which slow recovery of vision after OCAR has been described. Story⁹ in 1899 described 2 such cases. A 35-year-old man suddenly lost vision in the left eye to light perception (LP) which improved to counting of fingers (CF) and to

6/24 after 16 and 24 days respectively, and to 6/9 and 6/6 after 43 and 112 days respectively, with an ophthalmoscopically normal fundus. And a 39-year-old woman, who suddenly lost vision in the left eye, recovered to CF in 7 days and to 6/9 in 32 days. Werner¹⁰ described a 27-year-old syphilitic woman who, when seen 14 days after a sudden loss of vision in the left eye, was considered to have classical ophthalmoscopic findings of OCAR and doubtful LP. One week later the vision was LP in the superior nasal quadrant. One week after that she suddenly lost vision in the right eye with OCAR and was found to have doubtful LP in the right eye and CF in the left eye. The visual acuity in the left eye improved to 6/9 42 days after the occlusion and in the right eye to 6/12 and 6/9 14 and 20 days after the occlusion.

EXPERIMENTAL STUDIES

These are summarised in Table 2. There is a good deal of inconsistency in the results obtained, one report alleging irreversible retinal damage within 3 minutes, while in others much longer was needed. The relevance of those findings to clinical OCAR in man is open to criticism because of the following limitations in most of these studies.

Some of the animals used in these studies are not suitable for such an investigation; for example, rabbits have virtually no retinal circulation and the retina depends almost entirely for its nutrition on the choroidal circulation; cats have no central artery of the retina. The retinal ischaemia in these experiments was mostly produced by raising the

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Table 1 Previous clinical case reports of OCAR and recovery of vision

Author	Year	No. of eyes	Duration of ischaemia (hours)	Visual recovery to	Age	Cause of OCAR
Mauthner ¹	1868	1	1½	Normal	—	Embolus
Wood-White ²	1882	1	About 1	6/6	31	Embolus
Mules ³	1888	1	1	Normal	21	Embolus in inferior retinal artery
Wagenmann ⁴	1898	1	1/6	Normal	—	Spasm
Young ⁵	1932	1	About 36	Normal	70	Embolus
Orr and Young ⁶	1935	1	19½–27	Normal	—	Embolus in inferior temporal branch artery
Watson ⁷	1969	1	1/4	6/5	78	Arteriosclerosis
		1	1/2	6/9	53	Embolus
		2	2 and 2½	6/4	25	Orbital fracture
		1	4½	6/12	18	Not known
		1	6	6/36	65	Mild hypertension
		1	8	HM	75	Arteriosclerosis
		1	9	6/18	64	Thrombotic thrombocytopenic purpura
		1	13	6/36	42	Embolus
		1	14	6/18	18	Not known
		1	15	CF	65	Not known
		1	24	HM	26	Not known
		1	27	6/60	75	? Giant cell arteritis
		1	36	6/60	66	Mild hypertension
Younge and Rosenbaum ⁸	1978	1	About 2½	Normal	21	Embolus

CF = counting fingers. HM = hand motion.

Table 2 Previous experimental reports of acute retinal ischaemia and retinal tolerance time to ischaemia

Author	Year	Experimental animal	Experimental method to produce retinal ischaemia	Method used to evaluate retinal integrity	Tolerance time
Turnbull ¹¹	1948	Rat	Animal centrifugation	Histology	< 3 min
		Rat	Section of CAR	Histology	< 4–5 hr
		Rat	Asphyxiation of animal	Histology	< 3 min
Smith and Baird ¹²	1952	Rat	↑ IOP 100 mmHg	Histology	15 min
Popp ¹³	1955	Rabbit	↑ IOP 160 mmHg	ERG	> 60–< 75 min
Reinecke <i>et al.</i> ¹⁴	1962	Cat	↑ IOP 125 mmHg	Histology	< 1½ hr
Böck <i>et al.</i> ¹⁵	1963	Human	↑ IOP 200 mmHg	ERG	> 60–< 120 min
Fujino and Hamasaki ¹⁶	1967	Squirrel Monkey	↑ IOP to systolic BP	ERG and histology	60–< 90 min
Hamasaki and Kroll ¹⁷	1968	Squirrel Monkey	Nylon suture looped around CAR in orbit	ERG and optic tract discharges	> 90–< 210 min
Foulds and Johnson ¹⁸	1974	Rabbit	↑ IOP 10 mmHg above systolic BP	ERG and light and electron microscopy	Up to 1 hr
Johnson ¹⁹	1974				
Vassileva and Dabov ²⁰	1976	Rabbit	↑ IOP to supra-arterial level	ERG and retinal glycogen content	About 50 min
Shay and Ames ²¹	1976	Rabbit	Retina incubated in media lacking oxygen and glucose		40 min

BP = blood pressure. Hr = hours. IOP = intraocular pressure. Min = minutes.

intraocular pressure to supra-arterial levels, which not only stops the retinal circulation but also stops the choroidal circulation—the latter almost never occurs in the usual clinical OCAR in man. In almost none of these studies was there any systematic evaluation of the retinal circulation by fluorescein angiography. Finally, the retinal integrity was evaluated by electroretinography (ERG) and/or by histology. Our studies have clearly shown that ERG is not an entirely reliable technique for assessing retinal function after OCAR because it does not give us any information about the functional status of the ganglion cells or of most of the inner retina, which is essentially the area involved by OCAR in man.

Materials and methods

Our studies of experimental OCAR in 63 eyes eliminate these limitations by: (1) use of the rhesus monkey, which has a central retinal artery, retinal vasculature, retina, and other anatomical and physiological features identical to man's; (2) transient clamping of the central artery of the retina (CAR) at its site of entry into the optic nerve without interfering with the rest of the ocular circulation;²² (3) systemic evaluation of the retinal circulation by fluorescein angiography before, during, and after clamping the CAR and by fundus ophthalmoscopy;²² (4) evaluating the functional integrity of the retina not only by ERG but also by visual evoked response (VER), because the latter gives us information about the function of the retinal ganglion cells, optic nerve fibres, and the rest of the retina⁹ and in a number of animals even by testing the vision;²³ (5) using not only histological but also electron microscopic techniques to evaluate the morphological status of the retina;²⁴ (6) and finally, by using a large sample size (63 eyes) to discover the various biological variations in the response of retina to ischaemia.

Detailed accounts of our findings are given in the earlier papers of this series.^{22–24} Briefly these are as follows:

Ophthalmoscopic findings.²² These are summarised in Table 3. OCAR for up to 97–98 minutes did not produce significant permanent retinal or optic nerve damage except in 2 eyes (with OCAR for 75 minutes) which may represent a normal biological variation in response. However, OCAR for 105 minutes or more always produced irreversible permanent marked retinal and optic nerve damage.

Fluorescein angiographic findings.²² In all but 2 eyes with retinal ischaemia for up to 97–98 minutes the retinal circulation, after unclamping the CAR, remained perfectly normal throughout, with retinal

Table 3 *Ophthalmoscopic appearance at the end of the follow-up period*

Duration of ischaemia (minutes)	Follow-up period (weeks)	No. of eyes	Retina	Optic disc	Retinal vessels
16–20	12–22	11	Normal	Normal	Normal
75	1/2, 4, 22	3	Normal	Normal	Normal
	20	2	Atrophic	Atrophic*	Normal
90	12–14	3	Normal	Normal	Normal
97–98	17–19	4	Normal	Slight pallor*	Normal
105	13–16	4	Atrophic + + + normal-looking	Atrophic*	Narrow
134–138	13–14	3	Atrophic + + +	Atrophic*	Narrow
270–280	13–14	3	Atrophic + + +	Atrophic*	Narrow

*Started after 2 weeks and maximum by 3 weeks.

Table 4 *Pattern of recovery of ERG and VER after unclamping CAR*

Duration of ischaemia (minutes)	No. of eyes	Recovery time for	
		Normal ERG	VER present
90	6	5–40 minutes	1–3½ hours
97–98	8	15–60 minutes	Approx. 4 hours
102	2	1, 2 hours	2½, 4½ hours
	2	1½, 3 hours	No recovery
105	2	17 minutes, 3 hr	>3½ hours–<1 day
	4	5, 45, 75 min, 1 day	No recovery
135	6	2½, 3, 4 hours, 1 day, 1 day, ?	No recovery
270	5	b-Wave ½ normal	No recovery

capillaries normally outlined and no other angiographic abnormality. In eyes with retinal ischaemia of 105 minutes or longer and in 2 eyes with 75 minutes' OCAR the retinal capillaries and retinal pigment epithelium showed some atrophic changes.

Electrophysiological findings.²³ These are summarised in Table 4. These show that the ERG recovered to the normal level in all eyes with OCAR of up to 135 minutes, and the b wave was half normal with normal a wave in eyes with OCAR for 270 minutes. In contrast to these findings, the VER recovered to normal in all eyes (except 2) with OCAR up to 97–98 minutes and in 2 of the 4 eyes with OCAR for 102 minutes; in the rest of the eyes, i.e., 2 eyes with OCAR for 75 minutes, 2 eyes with 102 minutes, and all with 135 and 270 minutes' ischaemia, the VER did not recover. All the animals with OCAR for 97–98 minutes in their right eye and followed up

for 3–4 months had their normal left eye completely closed by a tarsorrhaphy; after this procedure the animals were found to behave normally, as if their vision had recovered in the right eye.

Morphological findings.²⁴ Light and electron microscopic studies revealed that OCAR for 105 minutes or longer resulted in irreversible damage to the inner part of the retina, including the inner two-thirds of the inner nuclear layer; the photoreceptors and outer part of the retina, including the outer one-third of the inner nuclear layers, were normal. The retina showed regional differences in susceptibility to ischaemia, the macular region being the most susceptible, the perimacular region less so, and the peripheral retina least of all. Differential susceptibility to ischaemia was also observed among various organelles and cells of the retina. Among the cytoplasmic organelles the mitochondria were found to be most susceptible, with microtubules and endoplasmic reticulum less so in descending order; the nuclei were the least susceptible of all. Among the retinal cells the ganglion cells were more susceptible than the bipolar cells, with Müller cells and astrocytic glia less susceptible, and the pericytes and endothelial cells of the vessels relatively resistant to ischaemia. The optic nerve showed atrophic degeneration of the nerve fibres. Eyes with OCAR for 97–98 minutes or less showed no appreciable permanent morphological damage in the retina and optic nerve.

Discussion

The data on our above-mentioned 4 types of findings^{22–24} were analysed, separately by the 3 different investigators and collated only at the end. It was most interesting that all of us arrived at virtually the same conclusion, that is, the retina can tolerate acute ischaemia for up to 97–98 minutes with full recovery in all eyes, with rare exceptions. All eyes with OCAR for 105 minutes or more suffer irreparable damage. Half of the eyes with 102 minutes' OCAR recovered visual function.

Our findings conflict with many of the anecdotal clinical reports (Table 1) and experimental reports (Table 2). The clinical reports by Mauthner,¹ Wood-White,² Mules,³ Wagenmann,⁴ and 2 by Watson⁷ (Table 1) agree with our findings. One of us (S.S.H.) saw a patient with OCAR who consulted an ophthalmologist and had his normal vision restored by a massage and paracentesis about 90 minutes after the onset of the visual loss. The patient has been followed up for 2½ years with normal visual fields and a visual acuity of 6/6. The present study casts serious doubt on the case reports

of recovery of vision many hours and even days and weeks after the onset of OCAR. It could be argued that in these patients there was sufficient residual retinal circulation after OCAR to protect against ischaemia; we investigated this topic particularly. Our findings were that there was no well-defined correlation between the amount of small residual retinal circulation and the severity of retinal damage. This subject is discussed in detail in Part I of this series.²² The discrepancies between the present study and some of the previous experimental studies (Table 2) may be due to the several limitations in those studies discussed above.

TERMINOLOGY

In connection with this subject it may be useful to distinguish the many terms used in the literature, e.g., survival time, recovery time, and tolerance or endurance time. Our definitions are as follows:

Survival time is the period during which after the onset of ischaemia there is still demonstrable function. (This has been reported as 4–5 minutes in rabbits¹⁸ and 5–15 seconds in man;^{25,26} this was not investigated in the present study.)

Tolerance or endurance time is the period of ischaemia after which function recovers completely, e.g., 97–98 minutes in our study.

Recovery time is the time taken by the retina to recover normal function after the restoration of normal circulation; this varied with the duration of ischaemia in our studies (Table 4), being about 4–4½ hours in eyes with 97–102 minutes' OCAR.

In the literature these terms are used interchangeably and confusingly.

COMPARISON OF THE TOLERANCE TIME TO ISCHAEMIA BETWEEN THE RETINA AND THE BRAIN

The findings of the present study also raise another very important question. In the brain permanent neuronal damage has been reported after ischaemia of 3½ (in cats²⁷) to over 6 minutes (in dogs²⁸), though recovery of some neuronal functions in cats had been reported 30 minutes after cardiopulmonary arrest.²⁹ In man cardiac arrest lasting for 3 minutes leads to permanent brain damage at 37°C, but at 28°C the brain withstands cardiac arrest for up to 7½ minutes.³⁰ Bourne³¹ concluded that cerebral ischaemia of up to 2 minutes is followed by full recovery, but even a small extension of this time produces permanent damage. Meyer³² recorded extensive neuronal necrosis in man following cardiac arrest under anaesthetic with ischaemia of 1 minute.

However, according to Garcia *et al.*^{33,34} although it has been held traditionally that ischaemia of a few

minutes' duration is lethal to brain tissue, the statement is not based on data derived from experimental scrutiny. Their biochemical and ultrastructural observations suggest that not only can mammalian brain seemingly endure prolonged incomplete ischaemia, but a serious breakdown of the system occurs only roughly 5 hours after the initial stroke.

It could well be argued that OCAR alone in man and primates represents an incomplete ischaemia of the retina, because the choroidal circulation remains normal and is not comparable to the complete global ischaemia of the brain. Experimental increase of intraocular pressure to above the arterial blood pressure level stops all intraocular circulations and produces 'global' retinal ischaemia and is comparable to the 'global' brain ischaemia. However, the available evidence (Table 2) does indicate that the retinal tolerance time to acute ischaemia is almost identical whether the ischaemia is produced by clamping the CAR alone (with normal choroidal circulation) or by raising the intraocular pressure to above the level of the arterial blood pressure (with arrest of both retinal and choroidal circulations).

In spite of the above mentioned findings by Garcia and others, clinical findings in man with complete global brain ischaemia and irreparable loss of cortical functions after about 3–7 minutes^{27 28 30–32} indicate that the tolerance time of the brain to ischaemia seems to be many times shorter than the retina's, though it has a similar neural structure. Naturally the question arises, why? To understand some of the factors responsible for this difference, it is essential to understand the mechanism of ischaemic damage to the neural tissue, which has been summarised very well by Dixon.³³

METABOLISM OF ISCHAEMIC NEURONES

For normal functioning, neural tissue requires 2 cardinal nutrients: glucose and an adequate supply of oxygen. There is considerable evidence that ATP and creatine phosphate (CrP) are the major high-energy compounds generated from respiration and glycolysis.³⁵ Ischaemia rapidly depletes the neurone of its stores of these compounds, thereby depriving the cells of the chemical energy so essential for maintaining both the electrical and synthetic activity of the cell. Aerobic oxidation can effect the synthesis of about 20 times as much ATP as is formed during anaerobic catabolism of the same quantity of sugar. Within about 10 seconds after the onset of complete ischaemia the oxygen of the brain is entirely consumed, leading to a sudden switch to anaerobic metabolism. It is supposed that the loss of consciousness in ischaemia is due to the fact that the cells do not have an adequate supply of

energy under anaerobic conditions. The most critical initial loss, therefore, is lack of oxygen and not of glucose.

METABOLISM OF ISCHAEMIC NEURONES IN THE RETINA

All the available studies on the subject have been conducted in rabbits only. Weiss³⁶ investigated the glycolysis in retinal ischaemia in rabbits. He found that rabbit retina normally has 0.05 mg glucose and 0.35 mg glycogen and the vitreous has 1.0–1.1 mg glucose and no glycogen, i.e., the glucose content of the vitreous is nearly 3 times higher than that of the retina. However, Wassilewa *et al.*³⁷ did find glycogen in the vitreous of rabbits (mean value of 350 $\mu\text{mol}/100\text{ g}$ in vitreous as compared to 2780 $\mu\text{mol}/100\text{ g}$ in the retina). In retinal ischaemia produced by raising the intraocular pressure to supra-arterial blood pressure levels Weiss³⁶ described the following changes: 'in the first 15–20 minutes of pressure ischaemia, the carbohydrate was taken up exclusively from the glycogen reserve of the retina. During the period of 20–40 minutes the glycogen content of the retina showed only a diminished decrease, about 30% of the value during the first 20 minutes. The reduction of the vitreous body glucose began simultaneously. It ranged within approximately the same limits as the utilisation of retinal glucose during the first 15–20 minutes. During the 40–70-minute period after the start of pressure ischaemia, the glucose reserve of the vitreous body was the only energy source for the glycolytic activity of the retina. Experiments extending beyond 70 minutes showed only slight sugar utilisation. When the experiment was extended to 2 hours, no significant difference was demonstrable between values after 90 and 120 minutes'.

If glucose-utilisation is taken as the indicator of anaerobic glycolysis in this experiment, then anaerobic glycolysis decreased during prolonged ischaemia. If it is assumed to be 100% in the first 15–20 minutes, it is 80–90% from 20–40 minutes, 70% from 40–60 minutes, 50% at 70 minutes, and 20–30% at 90 minutes' ischaemia. On restoration of retinal circulation after 1 hour of ischaemia the glucose of the vitreous remained constantly low in the first 30 minutes. One hour after the end of ischaemia it was replenished 80–90%, and an hour later it was normal. However, retinal glycogen was not replenished in this period, and only 2 days after the ischaemia did the glycogen reserve of the retina begin to renew itself; it was normal 24–36 hours after that. Intravenous administration of glucose did not affect the replenishment of retinal glycogen content in rabbits. These studies of Weiss³⁶ in rabbits showed that glucose taken anaerobically

from the vitreous is used up exclusively by the retina. He concluded that it is not the retinal glycogen but the glucose of the vitreous that must be regarded as the most important energy carrier in the retinal ischaemia lasting more than 20 minutes, and the exhaustion of the anaerobic glycolysis is one of the most essential factors determining the limits of tolerance time of the rabbits' retina. Ames and Gurian³⁸ and Webster and Ames³⁹ in incubated isolated rabbit retina found that either anoxia or glucose withdrawal alone produced less marked electrophysiological and electron microscopic changes than those produced by deprivation of both. Kaskel *et al.*⁴⁰ found that several intermediates of glycolysis were changed in their concentrations after pressure ischaemia of rabbit retina, indicating a shift from aerobic to anaerobic breakdown of carbohydrate. The high consumption of glucose in anaerobic glycolysis results in higher consumption of glycogen.^{37, 40} Vassileva and Dabov²⁰ found in rabbits that after 60–70 minutes' ischaemia complete replenishment of retinal glycogen did not occur, indicating irreversible change in the activity of enzymes which synthesise glycogen from blood glucose; they emphasised the great significance of glycogen in the retinal metabolism. Johnson⁴¹ found no glycogen in the Müller cells after 45–60 minutes' ischaemia in rabbits. Wassilewa *et al.*³⁷ found reduction in vitreous glycogen as well, though much less than in the retina. Oberhoff and Hockwin⁴² found that ATP content of the retina was decreased by 40% after 1 hour's pressure ischaemia in cat and rabbit eyes, and they assumed glycogen to be an energy store for the retina.

The suggestion that NAD⁺ concentrations may be of rate-limiting significance in the retina as well as in the brain is indicated by a related study of experimental microembolism in the miniature pig by Bardy and Tsacopoulos.⁴³ They found, histochemically, that oxidation reduction systems utilising NAD were not detectable following ischaemia. These authors also found a pH drop in the retina to 7.19 and then to 7.01 after 10 minutes. They ascribed this to diffusion into the retina of lactate accumulated in the vitreous. They speculated that this decrease in pH results in decrease in the activity of the phosphofructokinase system, a rate-limiting step in glycolysis, and eventually to cessation of cell function.

Although much more remains to be learned about the biochemical metabolic changes in the ischaemic retina, it is certain that an adequate supply of glucose and oxygen is vital for the normal functioning of the retina and that glycolysis is essential for its survival.

FACTORS RESPONSIBLE FOR MUCH LONGER TOLERANCE TIME TO ISCHAEMIA BY THE RETINA THAN THE BRAIN

Probably the following factors have an important role.

(1) The findings of Weiss³⁶ and others^{37–43} may help to explain the fact that the tolerance time of the retina is many times longer than that of the brain during ischaemia. The brain has very scanty stores of intracellular glucose and depends entirely on the blood circulation to supply constantly not only oxygen but also glucose. In contrast to that, in the retina, the situation is very different because (i) there is an ample store of glucose and glycogen, (ii) in addition, the vitreous's glucose content is nearly 3 times that of the retina, and (iii) probably the most important factor is that the major part of glucose and oxygen (80% and 60% respectively in pigs, and 80% of oxygen in cats⁴⁴) consumed by the retina ordinarily is delivered by the choroidal vessels.⁴⁵ This gives the retina self-sufficiency in glucose, and to some extent in oxygen, for a much longer time than the neurones in the brain. Weiss³⁶ found that in the rabbit retina, after 1 hour of ischaemia, there was still 0.15 mg of glycogen in the retina (0.35 mg in normal retina) and 0.60–0.65 mg glucose in the vitreous (1.0–1.1 mg normally). However, other similar studies in rabbits reported complete loss of glycogen in the retina following 45–60 minutes of ischaemia.^{20, 37, 41} The immediate loss of function in the retina (blindness) and in the brain (loss of consciousness) seem to be due to the deprivation of oxygen and show no difference between the 2 tissues.

(2) No-reflow phenomenon in ischaemic brain: The no-reflow phenomenon is the most accepted current view explaining the irreversible brain damage after a transient brain ischaemia. Development of marked oedema of the neural tissue in acute ischaemia is a well-known phenomenon. When this occurs in the brain, firstly the rigid cranial cavity cannot accommodate the extra volume produced by the oedema, and, secondly, since the brain as an organ is composed of thick, solid tissue, the deeper parts of the brain have no place to expand to in the surrounding solid, swollen tissue. Those 2 factors combine to cause obliteration of the microvasculature (since the vascular structures are the only pliable tissue which will yield and collapse as the neural tissue expands). This secondary vascular occlusion effectively prevents the return of the blood supply even if the circulation is quickly restored. The other factors which probably contribute to the no-reflow phenomenon in the brain are increased blood viscosity resulting from a shift of fluids from the extracellular to intracellular phase,⁴⁶ intravas-

cular sludging and clotting,⁴⁷ postischaemic rise in intracranial pressure,⁴⁸ and postischaemic hypotension.⁴⁹ Ames *et al.*⁴⁶ and others have shown that this local perfusion defect on restoration of circulation to the neural tissue (which may still be viable) produces irreversible damage.

The retina, on the other hand, is a very thin membrane set in surroundings which can accept oedema easily and regulate its pressure without compromising the retinal microvasculature, so that the phenomenon of no-reflow does not exist in the ischaemic retina. Hence the striking difference in tolerance times between the brain and the retina. It is conceivable that, if the neural tissue of the brain had a similarly favourable environment it could survive for a much longer time than it does.

(3) The other factor responsible for the retina's much greater tolerance of ischaemia than the brain's may be the difference in susceptibility to ischaemic damage by different types of neurones, as seen in the brain.²⁷ It is possible that the retinal neurones are more resistant to ischaemia than the neurones in the brain. Our studies²⁴ have shown that within the retina itself there is a differential susceptibility to ischaemic damage (*vide supra*). One of the possible reasons for the differential susceptibility between the different neurones may be the amount of protein turnover in a particular neurone. It has been shown that ischaemia inhibits cerebral protein synthesis,^{50,51} and this could explain the early and selective enzyme loss in certain areas of the brain. If an area has a high rate of protein turnover, it would be more susceptible to ischaemia. This would be especially true if increased proteolysis occurred, catalysed by lysosomal proteases released by cell destruction.⁵²

(4) Importance of the vitreous as a reserve source of oxygen for the retina: It could be argued that oxygen in the vitreous may play some role in the prolonged tolerance of the retina to ischaemia. Dr Albert Alm (Uppsala, Sweden), from various studies by him and his group (Anders Bill, Per Törnquist) on cats and pigs, calculated for us the amount of oxygen in the vitreous, which is most probably 2.4 μ l, corresponding to about 100 nmol oxygen (A. Alm, personal communication). Since the oxygen consumption of one pig retina *in vivo* is about 300 nmol/minute, the calculated oxygen in the vitreous could support normal retinal metabolism for about 20 second only. This would indicate that the vitreous can be disregarded as a significant source of oxygen in OCAR.

These are some possible reasons for the difference in the tolerance of ischaemia between the retina and brain, but there is much more to be learned before we can explain this mystery satisfactorily. This is an

important subject, because a better understanding of it could give us clues to increasing the tolerance of ischaemia not only in the retina but also in the brain, and thus help us to buy time for resuscitating these organs after acute ischaemia.

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Ischaemic optic neuropathy—a combined mechanism

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SUMMARY A clinical pathological study is reported of a patient who developed bilateral ischaemic optic neuropathy following a massive gastrointestinal haemorrhage with associated vascular complications in watershed areas of the myocardium and brain. Additional factors of giant cell arteritis and diabetic ketoacidosis contributed to the unique pathology. The distribution of infarction to the optic nerve has been related to known studies on the blood supply of the optic nerve.

Blindness following severe blood loss is well recognised, but few histopathological specimens have been obtained within a short time after such an episode.¹ Bilateral anterior ischaemic optic neuropathy has been observed following uncontrolled diabetes without acidosis and as a complication of diabetic hyperosmolar nonketotic coma.^{2–5} The following is a clinicopathological case report of a patient who developed sudden bilateral blindness and myocardial and cerebral infarction subsequent to massive gastrointestinal haemorrhage and diabetic ketoacidosis. The histopathology and distribution of ischaemic optic nerve changes will be described and related to both the antecedent vascular pathology and the blood supply of the optic nerve.

Case report

On 21 August 1977 an 82-year-old white female presented in the Emergency Department, complaining of blurred vision present for 3 days. Examination showed a best corrected vision of 20/60–, nuclear sclerotic and peripheral cortical lens opacities, mild corneal staining, and intraocular pressures of 10 mmHg in both eyes. She was alert, and the remainder of the examination, including pupillary responses and optic disc appearance, was unremarkable. Her blood pressure was 140/55 mmHg, with a regular pulse of 78/min. She was a known diabetic maintained on 23 units of NPH and 27 units of Toronto insulin daily. Her blood sugar was 302 mg/100 ml (16.8 mmol/l), urine showed +1 sugar and +1 ketones. The complaints were thought

to be related to her fluctuating blood sugar, so she was referred to her general practitioner for diabetic assessment and to her own ophthalmologist for continuing care.

The following day she was brought to the Emergency Department having been found at home unconscious and covered with bloody faeces. She was observed to be hypovolaemic secondary to gastrointestinal bleeding and severe ketoacidosis. Significant findings included absent bowel sounds, blood pressure of 90/50 mmHg, sinus tachycardia (96 per minute), left ventricular hypertrophy with strain pattern, and acute inferior myocardial ischaemia. Laboratory values included a blood sugar of 842 mg/100 ml (46.7 mmol/l), urinary 4+ ketones, pH 7.28, haemoglobin 7 g/dl, haematocrit HCT 24.5, leucocyte count of $19.9 \times 10^9/l$ (83% polymorphs) and platelet count of $529 \times 10^9/l$. She was treated with intravenous replacements including 4 pints (2.3 l) of packed red blood cells, insulin, potassium, a nasogastric tube, and antacids. Within 6 hours her clinical state improved, she regained consciousness, and was immediately aware of bilateral blindness. Her haemoglobin had risen to 12 g/dl and the leucocytosis persisted. Ophthalmic examination showed amaurotic pupils, no light perception, slightly cloudy corneae, intraocular pressures of 12 mmHg OU, normal motility with poor visualisation of the optic discs. The presumed diagnosis was bilateral ischaemic optic neuropathy secondary to hyperosmolar ketoacidosis and gastrointestinal haemorrhage. Temporal arteritis was considered, so a test of the sedimentation rate was ordered and 125 mg of methylprednisolone (Solumedrol) was given. Methylprednisolone was continued in regular doses of 25 mg intravenously 4 times a day.

Previous admissions to hospital had been for treatment of severe diabetic ketoacidosis, appendi-

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cectomy, hepatomegaly (biopsy confirmed minimal fatty vacuolation), and thoracic nerve herpes zoster. She had a history of diverticulosis and a rectal polyp was removed in 1963, as well as mild peripheral neuropathy, arteriosclerotic heart disease, and hypertension. Previous laboratory values included a slightly raised serum creatinine and a normal sedimentation rate, last recorded at 3 mm/h in March 1976. Six months prior to this admission her fluorescein angiograms showed minimal right macular oedema and a recorded vision of 20/80 right eye and 20/60 left eye.

On day 3 she was still in brittle diabetic control with frequent paroxysmal ventricular ectopic beats, and there was no evidence of fresh gastrointestinal haemorrhage. Her blood pressure was 100/60 mmHg, pulse 90, and respiratory rate 36 per minute. Ocular examination showed persistence of amaurotic pupils, no light perception, slight pallor of the optic discs, with minimal congestions of the retinal veins and a left 6th nerve palsy.

On day 4 her tachypnoea persisted, and a clinical diagnosis of acute pulmonary oedema secondary to fluid overload was made. Her visual status remained unchanged except for development of bilateral 6th nerve palsies. Her sedimentation rate was reported at 11 mm/h and steroids were totally discontinued.

On day 5 she developed an extensive right cerebral infarct with left hemiparesis and difficulty in swallowing. Her respiratory rate was 30 per minute, left pleural effusion was seen on x-ray, and she maintained a blood pressure of 140/80 mmHg. During the ensuing days her clinical course deteriorated, she developed a temperature of 38.5°C, and her haemoglobin and leucocyte counts remained raised. She never regained vision and she died 15 days after admission to hospital. Necropsy was performed within 24 hours of her death.

GENERAL NECROPSY

Post-mortem examination revealed a gastric ulcer overgrown with candida, which was the source of her massive gastrointestinal bleeding. In addition diverticulosis and a leiomyoma of the duodenum were noted, neither of which was responsible for the bleeding. Examination of the lungs revealed a terminal bronchitis. The heart showed extensive old scarring, and there were areas of necrosis in the posteroseptal region, with absorption of muscle cells, suggesting lesions 2 to 3 weeks old. The coronary arteries were patent throughout, though areas of atherosclerotic stenosis were observed, and microscopic sections showed intimal thickening. The larger vessels, including aorta, had severe atherosclerosis and calcification, while the arterioles of the kidneys, adrenals, and pancreas showed

hyalinisation. No evidence of giant cell arteritis was seen in any of the vessels. The hemiplegia was attributed to a massive right cerebral infarction, which undoubtedly was the most direct cause of her death. The infarct extended from frontal to occipital lobes, with additional widespread focal ischaemic changes throughout the brain, shown by minimal necrosis in the middle layers of the cerebrum. The 6th nerve palsies were ascribed to herniation secondary to brain swelling, as no infarctions were noted in the brain stem in the region of the nuclei.

In summary, this woman had poorly controlled diabetes with severe vascular complications of myocardial and cerebral infarction secondary to massive gastrointestinal haemorrhage.

OCULAR AND OPTIC NERVE EXAMINATION

Right and left globes, optic nerves, and surrounding vessels up to the orbital apex were examined. The globes were sectioned horizontally and processed with 1 cm of attached optic nerve on the right and 0.5 cm on the left. The remaining optic nerves and vessels were serially cross-sectioned. Macroscopically the globes were of normal size, and both showed posterior polar dot and blot haemorrhages with no significant disc abnormalities. A cotton-wool spot was noted below the superior temporal artery in the left eye. Sections were stained with haematoxylin and eosin, phosphotungstic acid, Holmes, periodic acid Schiff (PAS), Perls, elastic, luxol fast blue-haematoxylin-eosin, and Bodian stains.

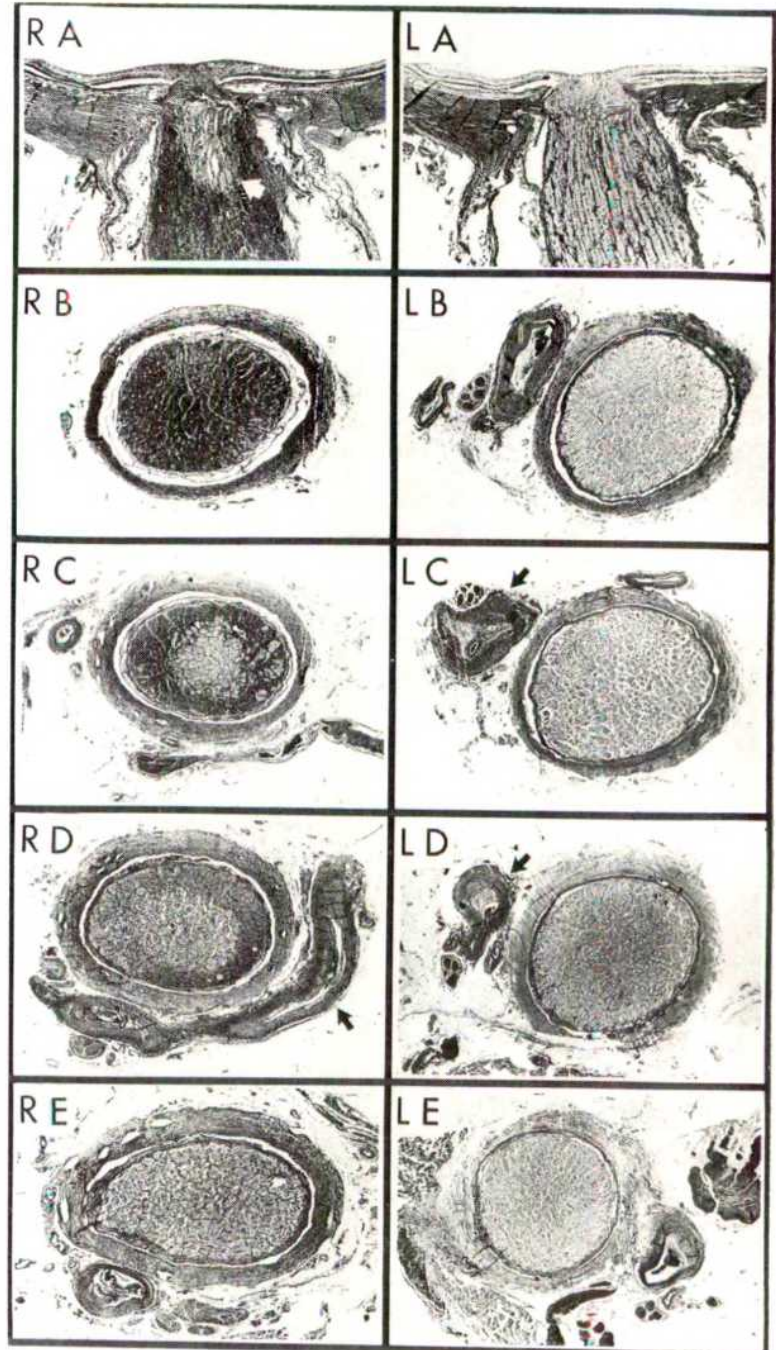
Microscopically both globes were characterised by minimal lacy vacuolation of the iris pigment epithelium, sclerosis of the sphincter muscle, atrophic hyalinisation with focal calcification of the ciliary body, and thickening of the basement membrane of the pigment epithelium. The lens had cortical degenerative changes, and the retina showed peripheral cystoid degeneration as well as equatorial and posterior polar haemorrhages in the inner nuclear and outer plexiform layers. Retinal arteriolar hyalinisation and thickening of the basement membrane of capillaries were noted.

The right optic disc was slightly oedematous, and there was a striking ischaemic infarct in the immediate retrolaminar area which gradually extended laterally to one side of the nerve with intact neuronal tissue immediately proximal to it (Fig. 1, RA and B). The proximal cross-sections of the nerve showed axial infarction which gradually extended peripherally to the pial sheath and involved the entire nerve (Fig. 1, RC, D, E). The axial changes consisted of varying distribution of focal nerve fibre bundle infarctions, some involving the total bundle and

others the centre of individual bundles (Fig. 2). In addition areas of infarcted neuronal tissue immediately adjacent to radial septa were observed (Fig. 2 inset). There was loss of astrocytes, nerve fibres, and myelin, with infiltration by macrophages laden

with engulfed luxol fast-blue and PAS positive material (Fig. 3). The right ophthalmic artery was characterised by marked fibroblastic proliferation of the intima, numerous multinucleated giant cells surrounding fragmented sections of internal elastic

Fig. 1 R—Right optic nerve. RA—Focal retrolaminar ischaemic infarction. RB—Intact neuronal tissue. RC—Axial infarction. RD—Extended infarction. RE—Total infarction. Arrows—narrow lumen of ophthalmic artery. L—left optic nerve. LA—Retrolaminar infarction. LB, C, D, E—Total nerve infarction. Arrows—narrow vascular lumen of ophthalmic artery. (Luxol fast blue and H and E stain, $\times 7.5$).



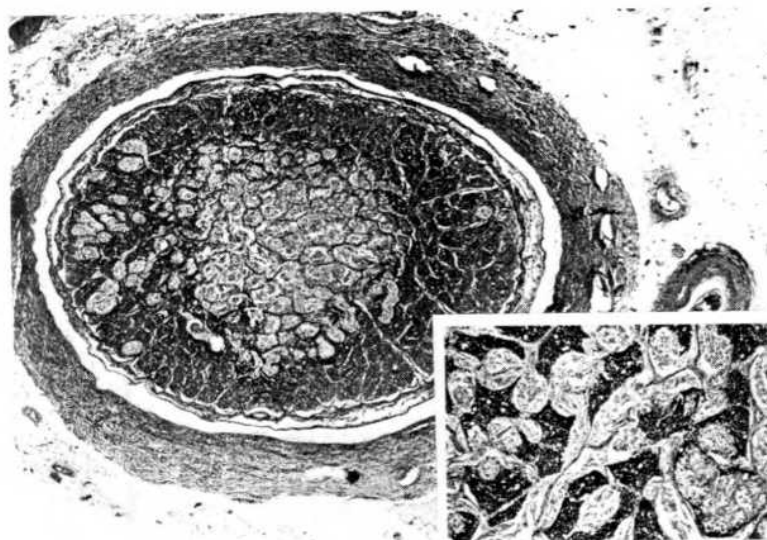


Fig. 2 Right optic nerve. Axial changes consisting of focal nerve fibre bundle infarction. (LFB and H and E, $\times 15$). (Inset: infarcted neuronal tissue adjacent to radial septa. LFB and H and E, $\times 25$).

lamina, haemosiderin laden macrophages, and lymphocytic and plasma cell infiltration of the media and adventitia (Fig. 4). The lumen, although narrowed, was not completely occluded at any point (Fig. 1, RD, E). The posterior ciliary arteries had subintimal fibrosis and thickening of the vessel walls.

The left optic nerve had focal evidence of retrolaminar infarction with preservation of cylinders

immediately proximal to it (Fig. 1, LA). The entire optic nerve was infarcted in cross-sections from 0.5 cm posterior to the globe to the apex of the orbit (Fig. 1, LB, C, D, E). The left ophthalmic artery illustrated similar histopathological inflammatory features as the right side, but anteriorly it was almost completely occluded (Fig. 5 and Fig. 1, LC, D arrows). That is, there was widespread destruction of internal elastic lamina, infiltration of the adventitia and media, multinucleate giant cells, and subintimal fibrosis. Neither the right nor left ophthalmic vessels showed an acute thrombus.

Discussion

Histopathological specimens of recent bilateral optic nerve infarction secondary to gastrointestinal haemorrhage have not been well described in the literature.¹ This clinicopathological report describes a patient with acute ischaemic necrosis of the heart, brain, and optic nerve following a haemodynamic crisis. We believe that watershed areas of the circulation, notably the middle layers of the cerebrum, the posteroseptal myocardium, and the retrolaminar optic nerve, were infarcted as a result of hypoperfusion-induced ischaemia. Additional pathology of giant cell arteritis, diabetic acidosis, widespread sclerotic vascular changes, and a possible hypercoagulation state are significant coincident factors in discussing the pathogenesis in this patient.⁶⁻¹⁰ The unique features of focal retrolaminar infarction immediately related to a zone of preserved neuronal tissue with proximal infarction may reflect on the vascular supply of the orbital optic nerve.

Clinical cases of simultaneous bilateral amaurosis

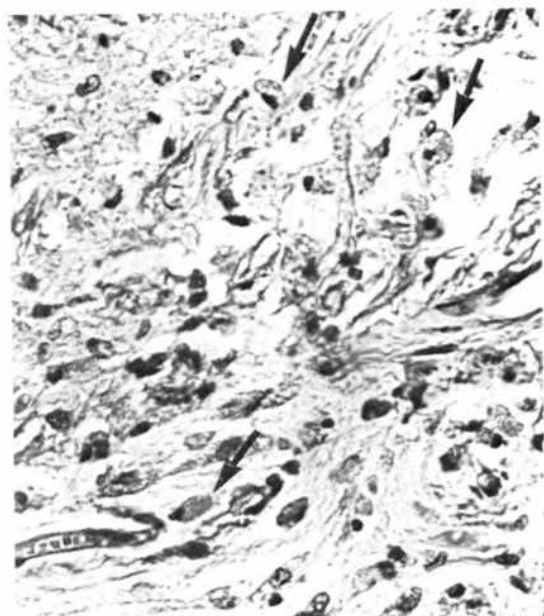
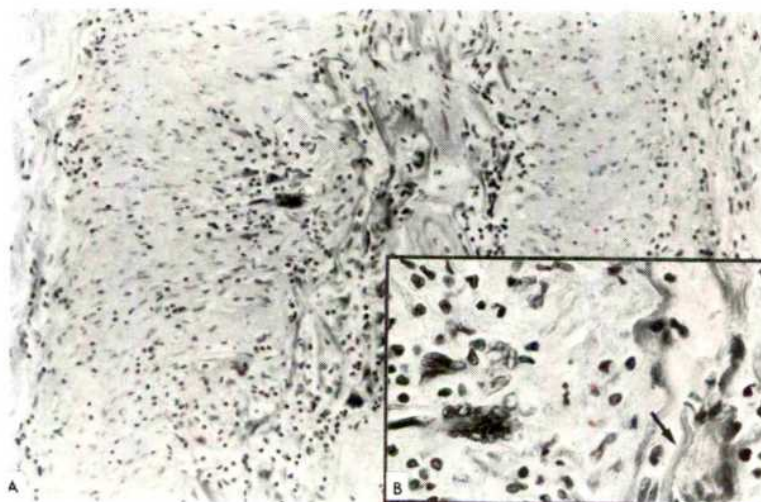


Fig. 3 Right optic nerve. Macrophages laden with engulfed PAS positive material (arrows). (PAS, $\times 18$).

Fig. 4A, B Right ophthalmic artery. Multinucleated giant cell surrounding fragmented sections of internal elastic lamina (arrow) (LFB and H and E, $\times 25$). (Inset $\times 24$).

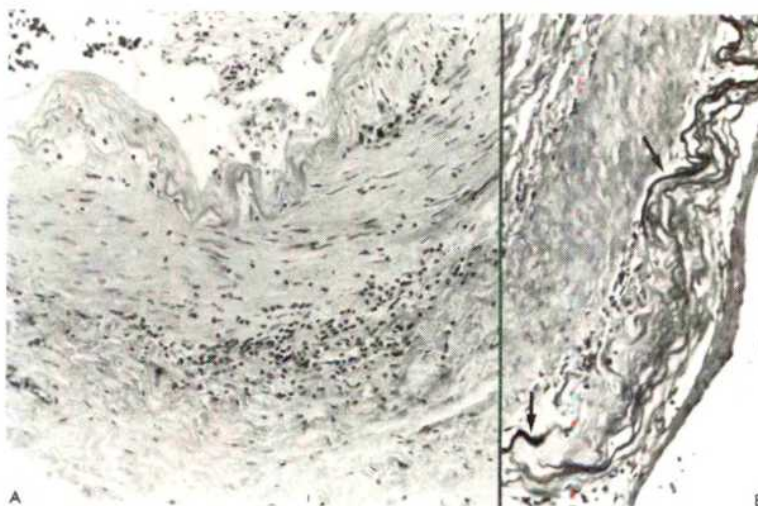


secondary to acute blood loss are well documented.^{11,12} The gastrointestinal tract is a frequent site of bleeding, and blindness occurs within 48 hours in about 50% of the patients.¹³ Clinical descriptions of the fundus after acute blood loss commonly note the presence of pale, oedematous discs with peripapillary flame-shaped haemorrhages and cotton-wool spots. Retinal arterial narrowing and tortuous congested veins may also occur.¹ Late changes included total optic atrophy or glaucoma-like cupping of the optic disc.^{6,10-15} Numerous authors note the particular vulnerability of the retrolaminar tissue to infarction when pathological processes involve the short posterior ciliary arteries.¹⁶⁻¹⁹ Hayreh²⁰ suggests that it is due to an imbalance between the perfusion pressures and the intraocular

pressure compounded by systemic hypotension. The presence of minimal clinical disc changes note in our case has been described previously by Spencer and Hoyt in cases of retrolaminar infarctions.¹⁸

Prior to the haemodynamic crisis the right ophthalmic artery was partially narrowed, whereas the left was almost totally occluded by the giant cell arteritic process. This was evidenced by multiple focal areas of degeneration of the elastic lamina, infiltration of lymphocytes, plasma cells, and giant cells involving the media and adventitia. The presence of intimal fibrosis, haemosiderin laden macrophages, and low grade inflammatory changes point to a long-standing arteritic process. In spite of this the patient's vision was recorded at the same level of 20/60 on the day before admission and for

Fig. 5 Left ophthalmic artery. A. Infiltration of media and adventitia by lymphocytes (H and E, $\times 15$). B. Fractured elastic lamina (arrows) (Weigert's elastic stain, $\times 15$).



at least 6 months before her haemodynamic crisis.

The presence of viable tissue proximal to the infarct, most notable on the right side, may be related to the anastomotic circulation in the anterior optic nerve and orbit.^{17 18 21} Collateral vessels between the internal and external carotid systems supplying the anterior orbit have been previously described. Further, it is suggested these collaterals are sufficiently large to take over when the circulation of the internal carotid is obstructed.²² The proximal right axial infarction reflects on the vulnerability of the central nerve, since it is supplied by an endarteriolar system (Fig. 1, RC).

Microscopically, the focal infarction of neuronal bundles reflects on 2 pathophysiological situations. The central infarctions suggest a collapse of the terminal capillary bed. The ischaemic necrosis along radial septa illustrates sectoral arteriolar collapse of the pial vessels (Fig. 2, inset).

A unique feature of this case is pathological evidence of giant cell arteritis involving the ophthalmic arteries alone without evidence in other anatomical sites.^{9 23} In addition our patient had a normal sedimentation rate even in the presence of hypovolaemia. A normal ESR has been previously observed in a minority of patients with ophthalmic giant cell arteritis.^{9 23}

The obvious question is whether the giant cell arteritis alone could account for the bilateral acute ischaemic nerve changes. We believe not, since bilateral simultaneous ischaemic optic neuropathy due to giant cell arteritis is very rare.^{9 23} In addition the nature of the ischaemia on the right side reflects both capillary and arteriolar collapse rather than sectoral obstruction, which is more characteristic of reported cases of giant cell arteritis. This hypothesis is supported by the clinical and pathological infarctions of the heart, brain, and optic nerves.

In summary, this patient had a massive gastrointestinal haemorrhage with vascular complications of myocardial, cerebral, and optic nerve infarction. Additional factors of giant cell arteritis and diabetic ketoacidosis contributed to the unique pathology.²³⁻²⁶ The distribution of optic nerve infarction has been related to known studies on the blood supply of the optic nerve.

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Photocoagulation in proliferative sickle retinopathy: results of a 5-year study

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SUMMARY The progress of proliferative sickle retinopathy (PSR) in 57 eyes treated by xenon arc photocoagulation has been compared with that in 41 comparison eyes. Angiographic assessment of the treated PSR lesions in 54 patients followed up for a mean period of 47 months (range 8-65 months) revealed cessation of leakage in 44 (81%), reduction of leakage in 8 (15%), and no change in 2 (4%). In the 41 comparison eyes more extensive perfused PSR occurred in 25 (60%), no change in 8 (20), and spontaneous improvement in 8 (20%). Autoinfarction of PSR lesions in comparison eyes was observed during the study period in 16 (39%). Assessed by visual acuity, there was no significant difference between treatment and comparison groups, deterioration of 3 lines or more on the Snellen chart occurring in 9% of the treated eyes and 5% of the comparison eyes. Vitreous haemorrhages occurred in 8 (14%) of treated eyes and in 7 (17%) of the comparison group. The most common complication of photocoagulation was choroidal neovascularisation in the burn area, choroidoretinal neovascularisation (CRN) occurring in 19 patients and choroidovitreous neovascularisation (CVN) in 12 patients. In 4 of the latter patients CVN lesions underwent rapid growth and in 4 were associated with vitreous haemorrhages. Other complications in the treated eyes included transient partial third nerve palsies, preretinal haemorrhage, haemorrhage confined to the burn area, vitreous haemorrhage, vitreoretinal traction, and retinal detachment. Statistical limitations of the present study dictate that the results be interpreted with caution. However, the complications of therapy, and the high prevalence of autoinfarction in the comparison eyes, indicate the need for a properly randomised study to define the role, if any, of photocoagulation in the therapy of proliferative sickle retinopathy.

Peripheral retinal capillary occlusion in sickle cell disease initiates a sequence of vascular events that may culminate in proliferative sickle retinopathy (PSR). Arising from arteriovenous anastomoses at the border of ischaemic retina, arcades of abnormal vessels grow out along the retina or project into the vitreous. As these arcades proliferate, they carry larger blood flows and are supplied by enlarged feeding arterioles and draining venules. These abnormal vessel systems leak fluorescein and plasma and may give rise to vitreous haemorrhage and either traction or rhegmatogenous retinal detachment. The risks of transient or permanent visual impairment have prompted attempts to render these lesions avascular by occluding the feeding arterioles

with xenon photocoagulation,¹⁻³ argon laser photocoagulation,³⁻⁵ diathermy,² and cryopexy.⁶ The techniques and preliminary results of xenon light coagulation in a group of Jamaican patients were reported by Condon and Serjeant,² and the results in a 5-year follow-up of this group are now presented.

Patients and methods

Patients were selected from the sickle cell clinic of the University Hospital of the West Indies. Of the 37 patients originally admitted to the study² 33 have been followed up for periods between 30 and 65 months, the remaining 4 patients having defaulted (2) or emigrated (2). Seven patients were added to the study in March 1974, 5 in December 1974, 6 in August 1975, and 6 in January 1977, bringing the total of patients to 57. At the last review, in July

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1978, patient follow-up varied from 8 to 65 months with a mean of 47.0 months.

There were 8 patients with homozygous sickle cell (SS) disease, 43 with sickle cell-haemoglobin C (SC) disease, 4 with sickle cell- β^+ thalassaemia ($S\beta^+$ thalassaemia) and 2 with sickle cell- β^0 thalassaemia ($S\beta^0$ thalassaemia). There were 33 males and 24 females with ages ranging from 13 to 64 years on admission to the study. The criteria used for haematological diagnosis were described by Serjeant⁷ and involved haemoglobin electrophoresis under alkaline and acid conditions, and quantitation of HbA₂ to differentiate SS disease from $S\beta^0$ thalassaemia.

Proliferative sickle retinopathy (PSR) was present on admission to the study or developed during the study bilaterally in 47 and unilaterally in 10 of the 57 patients. All eyes were treated in patients with unilateral involvement. In those with bilateral involvement the worst affected eye was treated in 41 patients and the less affected eye in 6 patients, in whom visual acuity in the worst eye was $<6/60$. The remaining 47 eyes in patients with bilateral involvement were followed up as a comparison group. Ophthalmological assessments as previously described⁸ were made during short-term visits (usually 3 weeks) at approximately yearly intervals by the visiting ophthalmologist (P.I.C.). Techniques of xenon arc photocoagulation using the O'Malley log. II photocoagulator included closure of the feeding arteriole and direct coagulation of the PSR lesion.² The draining venule was not directly coagulated. Retrobulbar anaesthesia was induced by injecting 2% xylocaine without epinephrine through a sharp 50 mm 25 g retrobulbar needle. The volume of local anaesthetic was routinely 3.5 ml, but variability in anaesthetic quality occasionally necessitated a volume of 5–6 ml for adequate anaesthesia.

The results of treatment were assessed by changes in dye leakage from the treated lesions, changes in visual acuity, and by comparing complications in the treatment and comparison eyes. Post coagulation angiographic assessments were generally performed 4–7 days after treatment.

Results

A total of 220 PSR lesions in the 57 patients were treated by xenon photocoagulation supplemented by diathermy in 8 patients. These included 33 lesions in SS disease (4.1 lesions/patient), 169 in SC disease (3.9 lesions/patient), 10 in $S\beta^+$ thal (2.5 lesions/patient), and 8 $S\beta^0$ thal (4.0 lesions/patient). The results in terms of fluorescein leakage from the treated PSR and complications of therapy



Fig. 1 Fluorescein angiogram of right temporal area in a 17-year-old female with SC disease (case 12) showing PSR lesion developing proximal to photocoagulation burn 1 year earlier.

are summarised in Table 1 and the visual acuities at the beginning and end of the study in Table 2.

LEAKAGE FROM PROLIFERATIVE LESIONS

Closure of feeding vessels and cessation of fluorescein leakage from the treated PSR lesions was achieved by one (41 patients) or more (5 patients) treatment sessions in 46/53 (87%) patients in whom post-therapy angiograms (4–7 days after treatment) were available. Leakage continued despite repeated coagulation in 4 patients (cases 26, 38, 42, 43), and additional therapy was not attempted in 3 patients (cases 7, 30, 41). After successful initial closure fluorescein leakage from retinal lesions recurred in 8 patients, being attributed to reperfusion of the original PSR lesion in 3 patients (cases 8, 16, 51) and to the development of new PSR lesions (Fig. 1) in 5 patients (cases 12, 15, 19, 31, 57). Further treatment of reperfused lesions was unsuccessfully attempted in 2 patients and not attempted in 1, and treatment of new PSR lesions was successful in the 3 patients in which it was attempted. In 2 patients (cases 24, 47) the extreme peripheral location of small PSR lesions did not allow attempted closure by the photocoagulator in use, but other lesions in both patients were satisfactorily occluded.

Fluorescein angiographic assessment at the end of study periods varying from 8 to 65 months (mean 47 months) was performed in all patients except 2 developing retinal detachment (cases 26,

Table 1 Clinical details, response to therapy, and complications in treatment group

Series cases	Age* sex	Eye treated	Number PSR lesions treated (D = diathermy)	Duration of follow up (months)	Final assessment leakage from treated PSR	Complications treated eye	Case in previous series ^a
<i>Homozygous sickle cell disease</i>							
1	20 M	L	3	46	Ceased	PVD, CRN	44
2	31 M	L	4	44	Ceased	Nil	—
3	34 F	R	1	65	Ceased	Nil	34
4	36 M	L	3	19	Ceased	Nil	—
5	48 M	R	9	44	Ceased	VRT	—
6	49 M	L	1 (D)	44	Ceased	Nil	—
7	56 F	R	5	8	No change	Nil	—
8	57 F	R	7 (D)	65	Improved	AU, VH, PVD, RT	13
<i>Sickle cell—haemoglobin C disease</i>							
9	13 F	R	3	46	Ceased	Nil	29
10	14 M	R	1	46	Ceased	VH, CVN	14
11	15 M	L	1 (D)	46	Ceased	3NP, AU, PRH, VH (2), VRT, CVN	8
12	16 F	R	5	65	Ceased	RHB (2), CRN	15
13	18 M	L	1	29	Ceased	CRN	25
14	18 M	L	2	65	Ceased	RHB (2), CRN	28
15	18 F	R	1	36	Unknown	Nil	—
16	18 F	R	6 (D)	53	Improved	Nil	—
17	21 M	L	1	65	Ceased	CRN	20
18	21 F	L	2	19	Ceased	3NP, CRN	—
19	22 M	L	1	19	Ceased	RHB, VH, CVN	—
20	23 M	L	6 (D)	65	Ceased	AU, PRH (4), CRN	10
21	23 M	R	7	65	Ceased	RHB (2)	27
22	24 F	L	4	29	Ceased	PVD, ERM, CVN	36
23	24 F	R	3	19	Ceased	CRN (2)	—
24	25 F	R	6 (D)	65	Ceased	ASI, PRH (4)	9
25	25 M	R	3	29	Ceased	CRN	17
26	26 M	R	7	46	Unknown	RD, VH	42
27	27 F	R	4	34	Ceased	RHB, CRN (2)	—
28	28 M	L	3	36	Ceased	CVN	—
29	28 M	R	5 (D)	65	Ceased	VH, ?CRN	11
30	28 F	L	10	19	Improved	Nil	—
31	28 F	L	2	46	Ceased	CRN	26
32	29 M	L	5	65	Ceased	RHB	16
33	29 F	R	2	53	Ceased	CVN	—
34	30 F	L	6	46	Unknown	3NP, RHB, RD	43
35	31 M	R	4	46	Ceased	CRN (2)	22
36	31 M	R	10	65	Ceased	CVN (3)	24
37	31 F	L	3	53	Ceased	3NP, CRN	—
38	32 M	L	8	65	Improved	PRH, VH (3), PVD, CVN	37
39	33 M	R	3	36	Ceased	Nil	—
40	35 F	L	3	65	Ceased	CVN	41
41	36 M	R	2	19	Improved	VRT, ERM	—
42	37 M	L	6	36	Improved	3NP	—
43	38 F	R	4	53	Improved	RHB, VH	—
44	40 F	R	1	65	Improved	RHB, CVN	21
45	41 M	R	4	9	Ceased	Nil	—
46	50 M	R	4	17	Ceased	Nil	—
47	51 M	R	8	65	Ceased	CRN	39
48	51 F	L	6	65	Ceased	Nil	19
49	55 F	L	1	36	Ceased	Nil	—
50	62 F	R	2	65	Ceased	Nil	18
51	64 M	L	3	53	No change	Nil	—
<i>Sickle cell—β^+ thalassaemia</i>							
52	19 M	R	2	65	Ceased	PRH, CVN	33
53	29 M	L	3 (D)	65	Ceased	AU, PRH (5), CRN	12
54	39 F	R	1	53	Ceased	CRN	—
55	62 M	L	4	65	Ceased	CRN	40
<i>Sickle cell—β^0 thalassaemia</i>							
56	27 M	L	5	65	Ceased	3NP, CRN	31
57	34 M	L	3	46	Ceased	3NP, CVN	32

Age* indicates age on admission to study.

Complications: 3NP = Partial third nerve palsy. AU = Anterior uveitis. ASI = Anterior segment ischaemia. RHB = Retinal haemorrhage confined to coagulation lesion. PRH = Preretinal haemorrhage. VH = Vitreous haemorrhage. VRT = Vitreoretinal traction. PVD = Posterior vitreous detachment associated with vitreoretinal traction. ERM = Epiretinal membrane. RT = Retinal tear. RD = Retinal detachment. CRN = Choroidoretinal neovascularisation. CVN = Choroidovitreous neovascularisation. (n) = n as suffix indicates number of lesions.

Table 2 Visual acuity measured on first and last attendance in treatment and control eyes, with probable cause of decreased acuity

Genotype	Patient no.	Eye treated	Visual acuity				Cause of decreased acuity in treatment (comparison) eye
			Treatment eye		Comparison eye		
			Start	End	Start	End	
SS	1	L	6/6	6/6	6/6	6/6	(Unknown) (Unknown) Unknown, (ERM) VH, (phthisis bulbi)
	2	L	6/6	6/6	6/6	6/6	
	3	R	6/9	6/9	6/9	6/9	
	4	L	6/18	6/18	6/6	6/12*	
	5	R	6/6	6/9	6/6	6/12*	
	6	L	6/6	6/6	6/6	6/6	
	7	R	6/6	6/12*	6/60	6/24	
	8	R	6/12	6/24*	NPL	NPL	
SC	9	R	6/6	6/6	6/6	6/6	VH Unknown ERM (VO) VO RD RD (RD) ? Macular oedema (RD) Bilateral VH (Phthisis bulbi) (Choroidal ischaemia) Cataract (VH)
	10	R	6/6	6/6	No PSR		
	11	L	6/6	6/6	No PSR		
	12	R	6/6	6/6	6/6	6/6	
	13	L	6/6	6/6	6/6	6/6	
	14	L	6/6	6/6	6/6	6/6	
	15	R	6/6	6/6	6/6	6/6	
	16	R	6/6	6/6	6/6	6/6	
	17	L	6/6	6/6	6/6	6/6	
	18	L	6/6	6/6	No PSR		
	19	L	6/6	6/12*	No PSR		
	20	L	6/6	6/12*	6/6	6/9	
	21	R	6/6	6/6	6/6	6/6	
	22	L	6/6	6/12*	CF	CF	
	23	R	6/6	6/6	No PSR		
	24	R	6/6	6/18**	6/6	6/6	
	25	R	6/6	6/6	6/24	6/24	
	26	R	6/6	<6/60**	6/6	6/6	
	27	R	6/12	6/6	No PSR		
	28	L	6/6	6/6	6/6	6/6	
	29	R	6/12	6/18	6/6	6/6	
	30	L	6/6	6/6	6/6	6/6	
	31	L	6/6	6/6	No PSR		
	32	L	6/6	6/6	6/6	6/6	
	33	R	6/6	6/6	6/6	6/6	
	34	L	6/6	<6/60**	6/6	6/6	
	35	R	6/6	6/6	NPL	NPL	
	36	R	6/6	6/60**	6/36	6/60	
	37	L	6/9	6/9	6/9	6/9	
	38	L	6/6	6/18**	6/12	6/60**	
	39	R	6/9	6/6	6/6	6/6	
	40	L	6/6	6/6	6/6	6/6	
	41	R	6/6	6/9	NPL	NPL	
	42	L	6/6	6/6	6/6	6/6	
	43	R	6/6	6/9	6/6	6/6	
	44	R	6/6	6/6	6/6	6/9	
	45	R	6/6	?	6/6	?	
	46	R	6/6	6/6	6/6	6/6	
	47	R	6/6	6/9	6/6	6/9	
	48	L	6/6	6/6	<6/60	<6/60	
	49	L	6/6	6/6	No PSR		
	50	R	6/6	6/6	6/6	6/6	
	51	L	6/9	6/18*	6/9	6/36**	
Sβ ⁺ thal	52	R	6/6	6/9	6/6	6/9	Unknown
	53	L	6/6	6/12*	6/6	6/6	
	54	R	6/6	6/6	No PSR		
	55	L	6/6	6/6	No PSR		
Sβ ⁰ thal	56	L	6/6	6/6	6/6	6/6	
	57	L	6/6	6/6	6/6	6/6	

*Deterioration in visual acuity of 2 lines or more and ** of 3 lines or more.

Abbreviations as in Table 1 except NPL = no perception of light; CF = counting fingers; VO = vitreous organisation

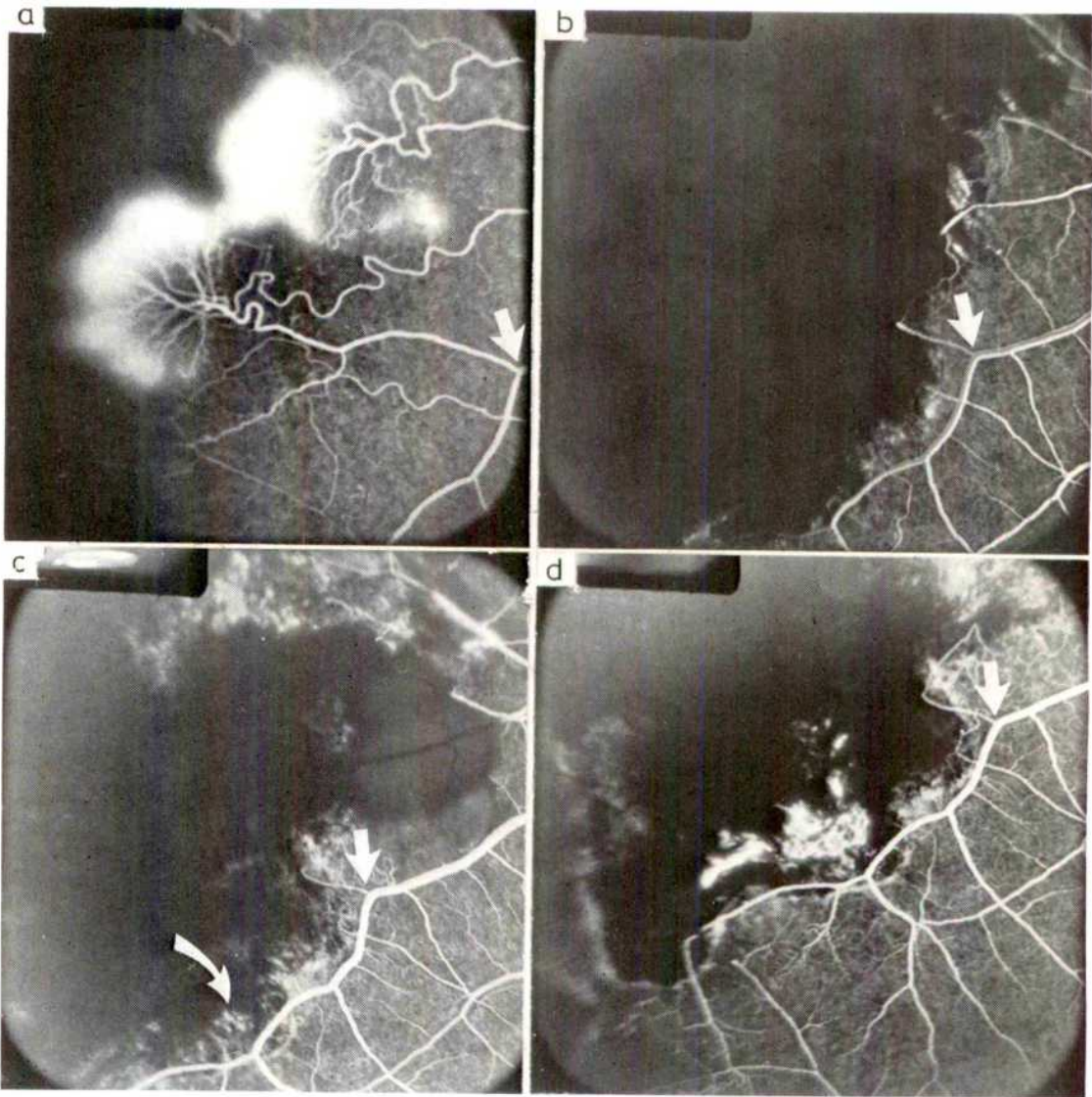


Fig. 2 Fluorescein angiograms demonstrating development of choroidoretinal neovascularisation in the right temporal area of a 27-year-old female with SC disease (case 27): same vessel junction marked by straight arrow. (a) Initial PSR lesion. (b) Two weeks after photocoagulation. (c) Nine months post treatment—major choroidal vessels visible and indicated by curved arrow. (d) Sixteen months post treatment—choroidoretinal neovascularisation.

34) and one who was pregnant (case 15). In the remaining 54 patients leakage from the originally treated PSR lesion was considered to have ceased in 44 (81%), improved in 8 (15%), and persisted unchanged in 2 (4%).

CHOROIDAL NEOVASCULARISATION

In 31 patients fluorescein leakage subsequently developed at the site of photocoagulation, all of

which showed fine vessel systems within the burn area apparently supplied by choroidal vessels and draining through either choroidal or retinal veins. In 19 patients these abnormal vessels were in the plane of the retina, and their fluorescence was separated from the surrounding normally perfused retina by a margin of nonfluorescence. These lesions were referred to as choroidoretinal neovascularisation (CRN), and an example is illustrated in Fig. 2.

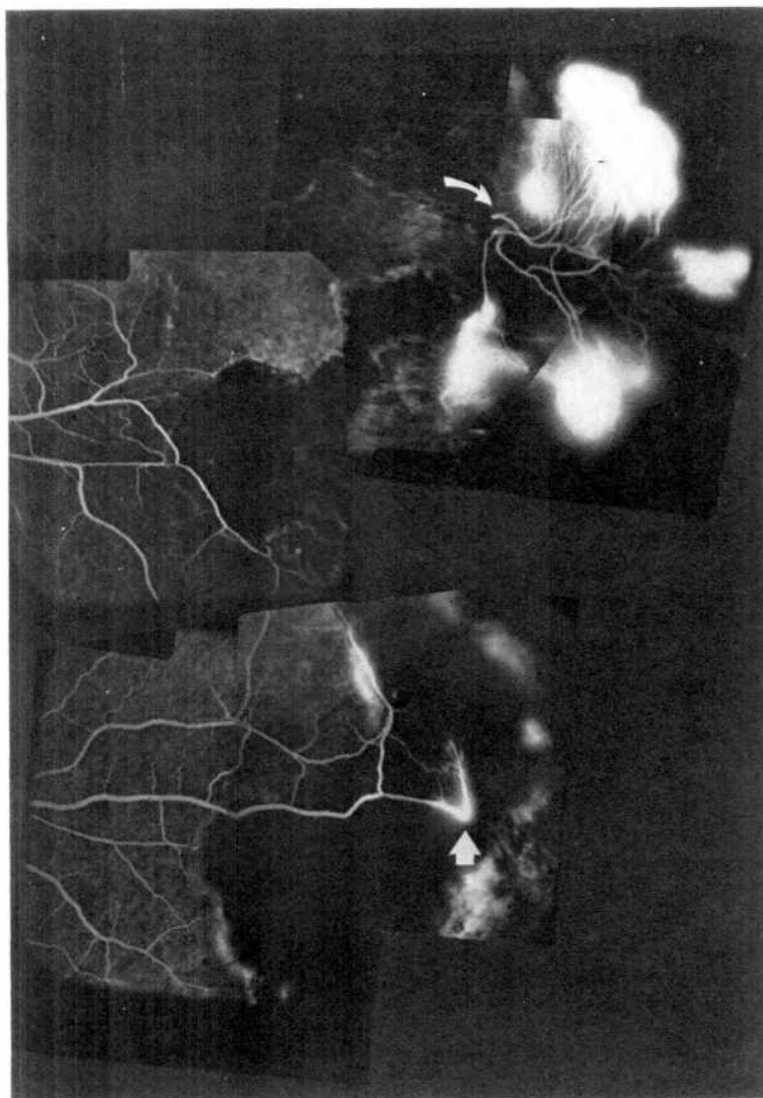


Fig. 3 Composite fluorescein angiogram depicting choroido-vitreal neovascularisation in the left temporal area of a 25-year-old female with SC disease (case 22) 28 months after photocoagulation. Lower arrow indicates coagulation site of principal feeder vessels for large PSR lesion. Upper arrow indicates site of chorio-vitreal neovascularisation.

In 12 patients the abnormal vessel system projected into the vitreous, and fluorescence from these lesions frequently overlay normal retina. These lesions were referred to as choroidovitreal neovascularisation (CVN), and an example is illustrated in Fig. 3. Four of the CVN lesions developed from CRN lesions during the period of follow-up, 2 apparently spontaneously and 2 after therapy of the CRN lesion. The remaining CRN lesions remained flat for follow-up periods of up to 54 months, did not enlarge, and did not give rise to complications. Choroidovitreal neovascularisation, however, underwent rapid enlargement in 5 patients (cases 11, 19, 22, 28, 33) and was associated with vitreous

haemorrhage in four (cases 10, 11, 19, 38). Photocoagulation of CRN lesions in 9 patients stopped fluorescein leakage in 3 (cases 20, 25, 35) and of CVN lesions in 7 patients stopped leakage in 1 (case 10).

HAEMORRHAGE

Preretinal haemorrhages occurred in 6 patients and were multiple in 3 patients, all of whom had received diathermy. Three patients (cases 20, 24, 53) developed haemorrhages in direct relationship to the diathermy burns, and two of these also developed preretinal haemorrhages in remote areas of the same eye. Two patients (cases 11, 52) developed

preretinal haemorrhages in relation to CVN lesions 4 years after therapy, and 1 patient (case 38) developed two preretinal haemorrhages, one as an extension of a deep retinal haemorrhage, 16 and 26 months after therapy. Retinal haemorrhage confined to the burn area occurred in 9 patients. Neither form of haemorrhage extended into the vitreous or affected visual acuity. Vitreous haemorrhage occurred in the treatment eye in 8 patients, 4 of whom had choroidovitreous neovascularisation. In 1 of these (case 10) a limited vitreous haemorrhage occurred during photocoagulation of a CVN lesion, but in the remainder the haemorrhage occurred 1½–3 years after therapy.

VITREORETINAL TRACTION

Vitreoretinal traction developed or became worse during the study in 7 patients. In 2 patients it was associated with epiretinal membranes and in 4 with posterior vitreous detachments. A retinal tear produced during therapy in one patient (case 8) was successfully sealed by further light coagulation at the same treatment session. Retinal detachment occurred in 2 patients both having had retreatment for a persistently perfused PSR lesion. In one (case 26) photocoagulation of a darkly pigmented area produced excessive heat release, with fracture of Bruch's membrane and an immediate subretinal haemorrhage which spread to the vitreous. This did not change for 1 month, but 4 months later a gradual blurring of vision occurred, and examination 1 year after the original treatment revealed no red reflex, no observable detail behind the lens, and inaccurate projection of light. The other patient (case 34) had apparently uneventful initial therapy but noted progressive deterioration of vision 1 year later, and examination 3 years after this revealed gross vitreoretinal traction and a total retinal detachment, which was unsuccessfully repaired with vitreoretinal surgery.

OTHER COMPLICATIONS OF THERAPY

Other complications in the treatment group included anterior uveitis, anterior segment ischaemia, partial third nerve palsies, haemorrhage, vitreoretinal changes, and retinal detachment.

Anterior uveitis occurred in 4 patients and settled promptly on systemic and topical steroid therapy. Anterior segment ischaemia occurred in 1 patient after scleral diathermy despite care being taken to avoid the long ciliary vessels or detachment of ocular muscles. This complication gradually settled on systemic and topical steroids, but signs of iris atrophy, irregularity of the pupil, and extensive anterior and posterior synechiae remained. Both anterior uveitis and anterior segment ischaemia were

confined to patients treated by scleral diathermy and were not considered complications of photocoagulation.

Partial third nerve palsies followed retrobulbar injection of local anaesthetic in 7 patients, all resolving satisfactorily within 2–3 weeks. There was the clinical impression that this complication was more common in patients requiring larger volumes of anaesthetic for effective anaesthesia.

BEHAVIOUR OF COMPARISON EYE GROUP

Of the 47 comparison eyes gross pathology precluded satisfactory longitudinal observations on PSR in 6. Four had retinal detachment (cases 8, 35, 36, 41) and 1 gross vitreous fibrosis (case 22) on admission to the study, and 1 patient (case 5) developed a gross vitreous haemorrhage after initial examination. Of the remaining 41 eyes 10 developed PSR for the first time during the study period, and an increase in the number or size of PSR lesions occurred in a further 21 patients. Autoinfarcted PSR lesions were present on admission to the study in 6 patients and developed during the study in 16, three showing complete autoinfarction of all leaking lesions and 13 a combination of autoinfarction and progression. When angiographic assessments were compared at the beginning and end of the study in the 41 comparison eyes with adequate data, 25 (60%) indicated more extensive perfused PSR, 8 (20%) showed no change, and 8 (20%) improved. In 3 of the latter patients PSR developed and spontaneously infarcted during the study period. The comparison group showed preretinal haemorrhages in 3 eyes and vitreous haemorrhages in 7 eyes. One vitreous haemorrhage (case 5) followed trauma to an eye with perfused PSR, the significance of which was difficult to assess.

Visual acuity, measured at the first and last attendance during the study, decreased by 2 lines or more on the Snellen chart in 12/57 (21%) of the treatment group compared to 4/42 (10%) of the comparison group. Deterioration of 3 lines or more occurred in 5 (9%) and 2 (5%) respectively and was attributed in the treatment group to retinal detachment (2), vitreous organisation (1), vitreous haemorrhage (1), and possible macular oedema (1), and in the comparison group to vitreous haemorrhage (2). The visual acuity in 1 patient in the treatment group (case 36) attributed to possible macular oedema subsequently improved to 6/12.

Discussion

The abnormal vessel systems that develop at the junction of vascular and avascular retina in sickle cell disease may compromise vision by causing

vitreous haemorrhage and/or retinal detachment. Rendering these lesions avascular appears logical, and their characteristic anatomy, with feeding arterioles and draining veins, makes them amenable to closure by localised coagulation. Xenon arc, argon laser, diathermy, and cryopexy have been employed, the present study using the xenon arc with supplemental diathermy in some cases. The procedure included coagulation of the feeding arterioles after their identification by fluorescein angiography, followed by coagulation of the proliferative lesion. Coagulation of the veins was not performed. The method and details of treatment of 33 patients in this series have been previously published.²

These methods are capable of stopping perfusion in most proliferative lesions. Condon and Serjeant² achieved closure in 91% of 36 eyes treated with predominantly xenon arc and Goldbaum *et al.*³ reported similar results in 53 eyes using either xenon or argon photocoagulation. However, the follow-up periods in these studies were relatively short, ranging from 2 weeks to 2½ years. The initial closure rate of 87% in the present study is similar to that in earlier series, 3 patients continuing to leak despite repeated photocoagulation.

The development of fluorescein leakage from vessel networks developing within the burn area complicated angiographic assessment of continued closure during follow-up. Noted initially as 'spot leakage' within the photocoagulation scar, fine networks of vessels developed, fed from the choroidal vessels and draining into either the retinal or choroidal veins. Two patterns of this choroidal neovascularisation were apparent. The term choroidoretinal neovascularisation (CRN) was used to describe vessel systems which lay flat in the plane of the retina and was not intended to imply anastomoses between choroidal and retinal circulations, although they frequently occurred. These lesions produced fluorescence within the burn area, which was usually separated by a margin of nonfluorescence from surrounding normally perfused retina. This abnormality has not been previously reported but has been noted elsewhere (Dr Lee Jampol, personal communication). Throughout follow-up periods up to 54 months these abnormal vessels generally did not enlarge or give rise to complications. The term choroidovitreous neovascularisation (CVN) was applied to vessel systems which invaded the vitreous and were originally reported as complications of argon laser therapy.⁵ The high prevalence of CVNs in the present study (22%) indicates that this is also a common complication with the xenon arc. These lesions tended to show progressive enlargement, and the association with vitreous

haemorrhage in 4 patients suggested that their natural history may be less benign than that of the CRN. Further coagulation therapy of these lesions was attempted in 7 patients, successfully stopping perfusion in 1, and it was interesting to note that rapid vitreous extension of a CVN in 1 patient was associated with decreased dye leakage compatible with spontaneous autoinfarction.

The aetiology of these lesions is unclear, though presumably related to breaks in Bruch's membrane caused by excessive energy release in the pigment epithelial layer. Reporting this complication following argon laser therapy, Goldbaum *et al.*³ attributed it to the high energy density associated with small (50–100 µm) burn sizes and suggested that this complication did not occur with larger burns (200–500 µm). These authors did not observe this complication with xenon arc therapy, in contrast to our own experience. Different techniques may have contributed to these different conclusions, Goldbaum *et al.*³ limiting coagulation to the feeding vessels whereas the PSR lesion was also coagulated in the present study. Since on several occasions a small apparently innocuous PSR lesion was replaced, after therapy, by a larger potentially serious CVN, this complication must be avoided if xenon arc photocoagulation is to play a part in the management of PSR lesions in these patients.

Certain complications attended repeated photocoagulation. Increased organisation and rigidity of the vitreous body with subsequent traction on the internal limiting membrane of the retina of the posterior pole occurred in 7 patients, 6 of whom had had 2 or more treatment sessions. Posterior vitreous detachment occurred in 4 patients, but traction retinal detachment was not observed. In 1 patient with 4 treatment sessions gross vitreous fibrotic changes occurred with vitreoretinal traction and recurrent vitreous haemorrhages originating in the choroid or deep retina peripheral to the coagulated area. Retreatment of a darkly pigmented area in another resulted in retinal detachment and blindness. To diminish these dangers the minimally effective power of the coagulator should be used in retreatment of pigmented areas.

Other complications related to therapy included transient partial third nerve palsies, anterior uveitis and anterior segment ischaemia, and haemorrhages. The duration of burn with the xenon arc photocoagulator used (1.5–3.0 seconds), necessitated the routine use of retrobulbar anaesthesia. Partial third nerve palsies which developed in 7 patients were probably related to the volume or siting of retrobulbar injections and all resolved satisfactorily. Anterior uveitis and anterior segment ischaemia were confined to patients receiving diathermy and

should probably not be considered complications of xenon arc photocoagulation. Multiple preretinal haemorrhages were also confined to the diathermy group. A single preretinal haemorrhage developed in 2 patients after xenon arc photocoagulation, but neither these nor the retinal haemorrhages confined to the burn area were of clinical significance.

Experience in the treated group must be compared with the behaviour of PSR in the comparison group during the study. Development or progression of PSR in 31 comparison eyes must be balanced against evidence of autoinfarction in 17 patients and complete cure in 3. Furthermore the rapid progression in some patients was not reflected in deteriorating visual acuity. There is some evidence that the most rapid progression of PSR occurs in the 15–30 year age group,⁹ which includes 27 (47%) patients in the present study, and it is therefore possible that longer term follow-up will be associated with more complete regression of PSR.

In terms of visual acuity measured at the first and last attendance there was no significant difference between treatment and comparison groups over a mean 4-year follow-up period. In terms of vitreous haemorrhage an episode occurred in every 26.4 years of observation in the treatment group compared to 21.4 years of observation in the comparison group. However, the failure to demonstrate a difference between treatment and comparison groups must be treated with caution in view of the statistical limitations of the study. When the study was started in 1973, it was felt that the response to xenon arc photocoagulation in this condition was

sufficiently unknown to justify treating only the worst affected eye. More data are now available, and if the problems of choroidal neovascularisation can be avoided there is a need for a proper randomly controlled trial of xenon arc therapy in PSR. With the realisation of the high prevalence of spontaneous autoinfarction, this study is especially necessary to define the role, if any, of photocoagulation in the therapy of these lesions.

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PARKE-DAVIS

Superficial reticular degeneration of Koby

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SUMMARY A 36-year-old white man with congenital ichthyosis and a history of a posterior uveitis beginning at age 8 presented with an unusual central corneal opacity. At age 26 bilateral central corneal opacities were noted consisting of fine interlacing white lines forming a reticulum at the level of Bowman's membrane. A faint brown background tint of the basal epithelium was also present. Over the next 10 years the opacity progressed only slightly, with some mild superficial scarring of the underlying corneal stroma. The visual acuity remained good. This corneal pattern appeared virtually identical to the superficial reticular degeneration of Koby. As described by Koby in 1927, this rare corneal degeneration is characterised as a painless, slow, progressive development of a central fine, white reticulum at the level of Bowman's membrane. This rare corneal degeneration probably represents an atypical form of band keratopathy.

Koby¹ described a progressive, superficial corneal degeneration in a middle-aged woman which led to a painless loss of vision. This condition was characterised by the appearance of a central fine white reticulum at the level of Bowman's membrane. The epithelium was thickened and bedewed, giving the appearance of a faint opalescence.¹⁻³ This slightly brownish discoloration provided a striking contrast to the white reticulum. There were no signs of inflammation. The loss of vision was progressive but rarely beyond 20/40.

After Koby's original description there was some disagreement concerning the true occurrence of such a case.³⁻⁶ Some authors thought that Koby's case represented lattice dystrophy,⁴ while others held that it was a distinct entity.^{3,6} This report presents a patient with the clinical signs of the superficial reticular degeneration of Koby.¹ The authors support the occurrence of this disease as a distinct entity which clinically resembles lattice dystrophy but lacks a positive family history, severe visual loss, and the presence of recurrent erosions.⁷ It is likely that the superficial reticular degeneration of Koby¹ represents an atypical form of band keratopathy.⁸

Case report

An 8-year-old white boy with the diagnosis of chronic vitreitis was referred to one of us (H.G.S.) in June 1950. There was a family history of congenital ichthyosis, but other past medical and family history was negative. The patient's entire body was affected except for both hands and face. At initial presentation a 6-month course of severe ocular inflammation had resulted in opacification of vitreous, which caused substantial visual loss. Fortunately the patient experienced only mild discomfort.

He was admitted to the University of Pennsylvania Hospital in June 1950, and a complete medical survey failed to reveal any other abnormalities. Ocular examination at that time showed that visual acuity was 6/30 in the right eye and 6/60 in the left eye. The intraocular pressure was normal in both eyes. The anterior segment was unremarkable. Both vitreous cavities showed milky-white, stringy opacities. The view of the posterior pole was blurred but seemingly normal. At the extreme periphery of the retina, especially temporally, large, yellow-white exudates extended from the retina into the vitreous. The clinical impression at the time suggested a chronic vitreitis, possibly of pars planitis type. Treatment was begun with adrenocorticotrophic hormone intramuscularly, and the opacities began

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to clear. In July 1950 the patient was referred to the Wilmer Institute, where another exhaustive medical and ophthalmological examination was performed. At that time the ACTH therapy had improved his vision to 6/9 in the right eye and 6/18 in the left eye. The large, yellow-white exudates were still present.

Over the next few years the patient was followed up at intervals never greater than 1 year. The visual acuity remained in the 6/12 to 6/18 range, and the episodes of inflammation became increasingly rare. Since 1964 there has been only 1 episode of inflammation.

In January 1963 a bilateral roughening of the corneal epithelium was noted. This was the first sign of any corneal change. At this time the visual acuity was 6/15 in both eyes, and there were no signs of any other ocular change. By March 1967 the cornea was noted to have a definite central opacity with a mosaic pattern, which was interpreted as being secondary to chronic inflammation and was thought to be a form of band keratopathy. At this time the visual acuity was 6/15 in the right eye and 6/18 in the left eye. By April 1968 the opacity had become more marked and the visual acuity had remained at the same level as the preceding visual acuity, 6/12 in the right eye and 6/15 in the left eye.

Over the next 6 years there was a slow but progressive bilateral increase in the opacities, and in 1975 the patient had well-defined corneal reticular patterns with some evidence of pigmented cells, which at the time were noted on the endothelium. The visual acuity was 6/9 in the right eye and 6/18 in the left eye. A new increase in the uveitis, limited to the left eye, was noted, as was the development of bilateral posterior subcapsular cataracts. In December 1978 at the time of his last examination the visual acuity was 6/12 in both eyes and applanation tension was 17 mmHg in both eyes. External examination showed no evidence of ichthyotic changes of the lids or periorbital. The result of the Schirmer's test with anaesthetic was 12 mm of wetting in each eye; without anaesthetic, wetting measured 16 mm in both eyes. Rose bengal and fluorescein patterns were normal, as was corneal sensation. A bilateral central corneal opacity with a faint brownish colour was noted at the level of the basal epithelium (Figs. 1 and 2). In this central area there was a well-defined, discrete, netlike pattern of interlacing fine white lines at the level of Bowman's membrane (Figs. 3-6). By scleral scatter the fine white lines appeared light brown (Figs. 4 and 6). The underlying superficial stroma appeared slightly scarred. Descemet's membrane was normal, and there was a mild amount of pigment deposited on the endothelium. The lens and retina could easily be seen through the opacity, which was limited to

the central cornea in both eyes. There was no evidence of peripheral band keratopathy. The lens showed early posterior subcapsular cataracts in both eyes. The vitreous showed numerous large opacities in both eyes, and the posterior pole appeared normal. It is our impression that this patient had the superficial reticular degeneration of Koby,¹ which may represent an atypical form of band keratopathy.

Discussion

Information on superficial reticular degeneration of Koby¹ is scarce, especially in recent publications,⁵ which leads to scepticism in terms of the occurrence of this entity as a true corneal dystrophy. Only one pedigree has been reported, a full 20 years after the original description.⁵ The possibility that this patient may have represented a pedigree of lattice dystrophy is likely in view of the finding in several other family members of recurrent erosions, a prominent feature of lattice dystrophy⁷ but one that has not been described in the superficial reticular degeneration of Koby.^{1,3} We are then left with several isolated occurrences, most of which were associated with chronic ocular inflammation. All these factors suggest that we are dealing with an unusual type of corneal degeneration. This is also likely in view of the fact that most patients with this type of corneal change have either been middle-aged or had long periods of chronic ocular inflammation. Furthermore, in his original description Koby¹ used the term degeneration. For this and other reasons we support the designation of this entity as the superficial reticular degeneration of Koby¹ and have used this term throughout this report. As to the specific type of degeneration, it appears clinically to resemble an atypical form of band keratopathy.⁸

The white linear appearance at the level of Bowman's membrane suggests an atypical form of band keratopathy. This is in keeping with the occurrence in some eyes of longstanding inflammation. The opalescence of the brown background tint of the epithelium is more difficult to explain. In cases of recurrent erosions we find irregular iron lines as evidence of chronic tear film disruption. These iron lines impart an irregular yellow-brown tint to the central epithelium. This tint is usually discrete and linear. In this unusual degeneration, we noted an accumulation of pigment at the level of the basal epithelium similar to that seen in Fabry's disease or chloroquine toxicity^{9,10} except that the distribution of the pigment is not whorl-like but reticular and diffuse. This brownish pigment extends just beyond the limits of the reticulum and is

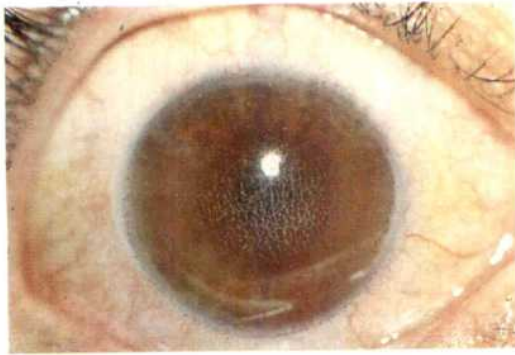


Fig. 1 Right eye. Reticular pattern covering pupillary axis.

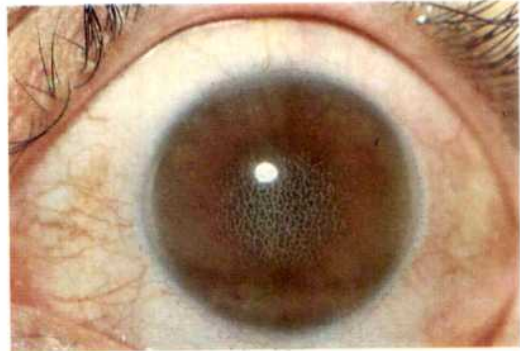


Fig. 2 Left eye. Central reticular pattern appearing identical to that of right eye.



Fig. 3 Right eye. Slit-lamp view showing superficial location of reticulum at Bowman's membrane with mild underlying stromal scarring.

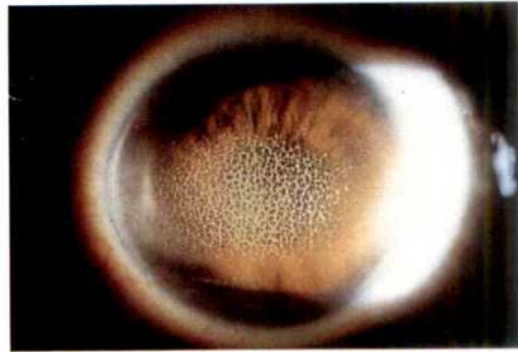


Fig. 4 Left eye. High-power scleral scatter showing fine reticular pattern appearing light brown.

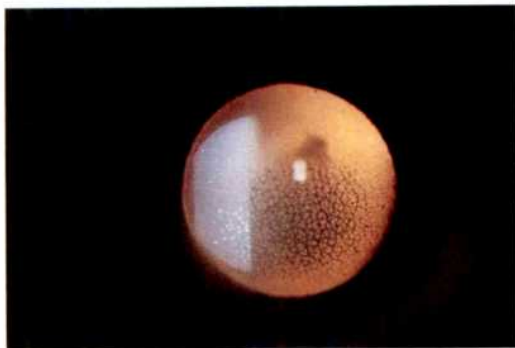


Fig. 5 Right eye. Red reflex view of reticulum in central cornea showing limits of corneal involvement.

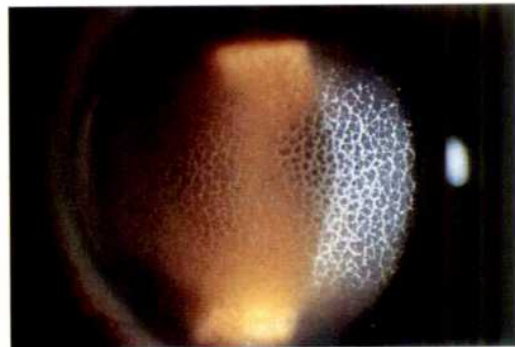


Fig. 6 Left eye. High-power slit-lamp photograph highlighting white-appearing reticulum with direct light and light brown pattern with indirect light.

unique to this corneal degeneration. We are unable to explain the way in which this pigment distribution occurred or its exact nature.

One of our chief initial speculations was that this particular corneal pattern might represent a manifestation of congenital ichthyosis. Numerous authors have reported cases of various corneal manifestations of congenital ichthyosis. These fall into four main groups:¹¹⁻¹⁴ (1) superficial, round, elevated nodules which have been likened to Salzmann's nodular degeneration and indeed in 1 case were shown to be histopathologically identical to this entity;¹³ (2) forms of typical band keratopathy which are usually secondary to exposure due to the cicatricial ectropion commonly found in patients with the facial manifestations of congenital ichthyosis;¹¹ (3) a superficial, discrete, subepithelial opacity which may or may not be accompanied by a form of typical band keratopathy;¹³ and (4) a discrete, deep, pre-Descemet's membrane opacity that is linear and seedlike in appearance, and usually found as an isolated occurrence.¹⁴ This form is more commonly found in sex-linked ichthyosis. No previous article on ichthyosis reports any change similar to that which occurred in our patient. Therefore it seems unlikely that this patient's corneal appearance could be ascribed to congenital ichthyosis.

Clinically the differential diagnosis must include lattice dystrophy, since the pattern of this delicate network of white lines mimics the typical lattice pattern. It is only with careful slit-lamp examination that the lines in superficial reticular dystrophy of Koby¹ can be noted to be limited to the level of Bowman's membrane and lack the birefringence seen in lattice lesions. Of course the lack of family history, severe progressive visual loss, and symp-

toms of recurrent erosions all argue against the diagnosis of lattice dystrophy.

In conclusion, we surmise the superficial reticular degeneration of Koby¹ to represent an atypical band keratopathy.

We thank William C. Nyberg for ocular pathology and S. Flavia Blackwell for editorial assistance.

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Abnormal intraocular pressure control in systemic hypertension and diabetic mellitus

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SUMMARY Retinal vein obstruction is a common complication of the retinopathy seen in patients with chronic hypertension. Previous studies have shown an abnormal control of intraocular pressure in response to changes of posture in patients with retinal vein obstruction. This paper describes the results of the investigation of the intraocular pressure response in 57 normotensive healthy adults and in 95 hypertensive patients, with a short study of 14 diabetic patients. Both hypertensive and diabetic groups showed abnormal responses. The possible significance of these findings as the expression of a fundamental anomaly shared by patients who develop either hypertension or diabetes is discussed.

In a previous communication we reported our finding that patients who have suffered a unilateral obstruction of a central or tributary vein have a bilateral defect in the regulation of their intraocular pressure when they are subjected to a change in posture.¹ We found that, whereas our control subjects, who had not suffered a retinal vein obstruction, maintained a relatively constant pressure in both their eyes when they changed from the sitting to lying position, our patients showed a bilateral rise in pressure. Thus in the subjects we examined the mean rise in pressure recorded in a group of nonobstructed eyes was 0.6 ± 1.2 mmHg, while that recorded in the eyes of patients with a central retinal vein obstruction was 1.8 ± 2.4 mmHg in the eye with the lesion and 2.6 ± 2.3 mmHg in the contralateral eye. Similarly, in the eyes of patients with a tributary vein obstruction the rise in pressure was 3.1 ± 2.3 mmHg in the obstructed eye and 2.1 ± 2.2 mmHg in the contralateral eye. (In this series of experiments both sitting and lying pressures were recorded after the subject had been in the relevant position for 15 minutes.)

We remarked on 2 aspects of our results which seemed to us to be of particular interest: (1) the response shown by our patients was in some ways similar to that shown by patients with primary open-angle glaucoma; (2) the abnormal response was shown by both eyes and not only by the eye with the obstructive lesion.

The first of these facts was interesting because there is a marked clinical association between open-angle glaucoma and retinal vein obstruction, many patients with the latter condition developing this type of glaucoma in one or another eye.^{2,3} This suggested to us that eyes which develop open-angle glaucoma and those which develop venous obstruction may share a common defect which predisposes them to one or both of these conditions.

It seemed to us that the abnormal rise in pressure we had found must be due either to a defect in the outflow of fluid from the eye or to a relative increase of the intraocular contents (the globe being considered as a more or less inelastic container). We therefore proceeded to compare the drainage potential of both eyes in a group of patients with a unilateral retinal vein obstruction using the Alcon Pneumatograph. Our tonographic results showed no correlation between the value of the coefficient of outflow and the magnitude of the rise of intraocular pressure occurring in any eye when the patient changed to the lying position and no correlation between the relative values of the coefficients of outflow in any pair of eyes and the occurrence of the obstruction in one eye or the other.⁴ These results are in agreement with others,^{2,3} and we concluded that the postural rise of intraocular pressure is not dependent on impairment of drainage from the anterior chamber.

Our belief that this abnormal response to posture is the measure of an underlying anomaly which may predispose eyes to the development of a venous

obstruction was strengthened by the second feature of our results to which we referred, namely, the abnormal response was bilateral. While we did not neglect the possibility that the behaviour of the contralateral eye might be explained as some sort of sympathetic effect resulting from changes in the eye which was the site of the lesion, it seemed more likely that the bilateral response might in fact represent such an underlying condition which, with time, had led to an overt obstruction in one eye.

In our original communication, we described retinal vein obstruction as a 'major complication of the retinopathy seen in patients with systemic hypertension'. Certainly hypertensive patients form a large and distinct group of patients presenting with this lesion, and the retinal changes associated with chronic hypertension, namely, fat veins with a marked arteriovenous crossing phenomenon, are the background on which the picture of an obstruction so often supervenes.

We therefore decided to carry out the postural test on a small number of randomly selected patients from the hypertension follow-up clinic at St Mary's Hospital, London, as an initial study and to proceed to a larger investigation if the results suggested this was worthwhile.

Pilot study

We selected 12 patients, irrespective of age, sex, race, the aetiology, duration, or magnitude of their hypertension, and of whether they were receiving therapy; that is, we used the same criteria for selection as we applied to the selection of patients with venous obstruction in our original studies. We made an arbitrary definition of hypertension as that existing when any subject had a systolic pressure of 150 mmHg or higher and a diastolic pressure of 90 mmHg or higher on more than one occasion. We examined 6 men and 6 women. Their ages ranged between 29 and 60 years with a mean value of 45.5 ± 10.6 years. Their systolic pressure ranged between 110 and 230 mmHg and their diastolic pressures between 82 and 145 mmHg, with a mean value of 164 ± 42 mmHg and 103 ± 20 mmHg (these pressures were recorded with the patients in the sitting position, the diastolic pressures being read at phase 4).

Method

Each subject was asked to sit quietly on a couch for 15 minutes, during which time the fundi were examined and a note was made of the state of the disc, veins, arteries, and arteriovenous crossings.

Two drops of oxybuprocaine 0.3% and fluorescein 0.125% eye drops were then instilled in both eyes and the intraocular pressure measured with a Perkins hand-held applanation tonometer, the reading being taken when the insides of the half rings just touched in the diastolic phase. The right eye pressure was always measured first. Three rapid measurements were made and recorded for each eye. The subject was then asked to lie down (with one pillow under the head) and after 15 minutes the intraocular pressures were measured as before. All measurements were made by one observer (B.I.W.). Normally the 3 readings on the tonometer differed by no more than 0.5 mmHg and frequently they were identical. In those unusual cases where there was more than 1 mm difference in the readings further rapid measurements were made until 3 readings differing by no more than 0.5 mm were obtained, and these were used.

Results

The mean rises recorded varied between 0 and 8.5 mmHg with an overall mean value for the group of 3.5 ± 2.5 mmHg. Since these values are of a higher order than those we found for the groups of control patients in our initial experiments, we decided to carry out a larger and more detailed study of hypertensive patients.

Main study

Protocol

The information we wished to obtain from this study was as follows:

(1) Could we confirm our values for the control response to the postural test in a larger group of healthy normotensive adults? (2) Does the rise of intraocular pressure on lying in a group of randomly selected hypertensive patients differ from that in the control subjects? (3) Is there any relationship between the magnitude of the response to the postural change in any control or hypertensive subject and factors such as change in systemic arterial pressure, certain features observed on funduscopy, family history, personal medical history, or drug taking, including smoking and alcohol. (4) Is there any difference in the result of the postural test if the intraocular pressure is recorded at 0 min, that is, as soon as possible after the subject lies down, as opposed to 15 min? We designed our experiments with these questions in mind although our data were inevitably incomplete in certain respects for certain patients.

Method

CONTROL SUBJECTS

This study was carried out at the Wellcome Research Laboratories, Beckenham. The subjects were all staff members who volunteered to have their intraocular pressure measured. All these volunteers received a preliminary examination by one of us (E.L.), who filled in a questionnaire with respect to age, sex, race, smoking and drinking habits, any tablets, pills, or medicines taken (including contraceptive tablets in the case of women), past and present medical history, and a family history which questioned specifically the occurrence of hypertension, coronary artery disease, stroke, renal disease, 'toxaemia' of pregnancy, diabetes, glaucoma, or other diseases. He measured their blood pressure (sitting position) and carried out a routine urine analysis to exclude proteinuria or glycosuria. As previously (in the pilot study) an arbitrary value of 150/90 mmHg was taken as the dividing point, and any subject with either a systolic value or a diastolic value greater than these on more than one occasion was excluded from the control group. However, all volunteers were included in the study carried out by B.I.W., who had no previous knowledge of the results of this preliminary investigation by E.L. The study was therefore blind. Four volunteers were found to be hypertensive, 1 diabetic (with background retinopathy), and 1 had chronic uveitis with secondary glaucoma. They were excluded from the control group, the hypertensive subjects being transferred to the hypertensive group. We were left with 57 control subjects as a result of this procedure.

The values for sitting blood pressure found on the 2 occasions by E.L. and B.I.W. were compared by Duncan's multiple range test. The observations made by the 2 investigators were closely correlated.

Systolic blood pressure. Correlation coefficient (r)=0.62, $P<0.001$.

Diastolic blood pressure. Correlation coefficient (r)=0.67, $P<0.001$.

We examined 37 females and 20 males. Their ages ranged between 18 and 65 years with a mean value of 34.5 ± 13.1 . Their mean arterial pressures were 114.7 ± 11.5 mmHg and 74.3 ± 8.3 mmHg (sitting position, diastolic pressure recorded at phase 4). Each subject was asked to sit quietly for 15 minutes on a couch. The arterial pressure was then recorded twice with a random zero sphygmomanometer. Two drops of oxybuprocaine 0.3% and fluorescein 0.125% were instilled in each eye, and the intraocular pressure was measured with a Perkins hand-held applanation tonometer by the same criteria as already described above. The subject was then asked to lie down from the sitting

position (one pillow), and the intraocular pressure was once more measured in the same way, as soon as possible, that is, within the first minute. After the subject had been lying down for 15 minutes the systemic arterial and intraocular pressures were once more measured as before.

HYPERTENSIVE SUBJECTS

We examined 95 hypertensive subjects by a procedure precisely similar to that adopted for the controls. All the subjects included in the hypertensive group had a systolic pressure greater than 150 mmHg or a diastolic pressure greater than 90 mmHg recorded on more than 1 occasion.

We examined 46 females and 49 males. Their ages ranged between 18 and 80 years with a mean value of 49.3 ± 14.4 years. Their mean arterial pressures were 147.5 ± 24.1 mmHg and 98.8 ± 12.8 mmHg (sitting position, diastolic pressure recorded at phase 4).

Results

INTRAOCULAR PRESSURE (FIGS. 1 AND 2 AND TABLE 1)

(1) All the mean values for intraocular pressure fall within the normal range, irrespective of the position in which they were measured or the group to which the subject belonged, that is, 20 mmHg or <20 mmHg. (2) There was no significant difference, within either group, between the right and left intraocular pressures irrespective of the position in which they were measured. (3) There was no significant difference between the mean intraocular pressure of the 2 groups when measured with the patient in the sitting position.

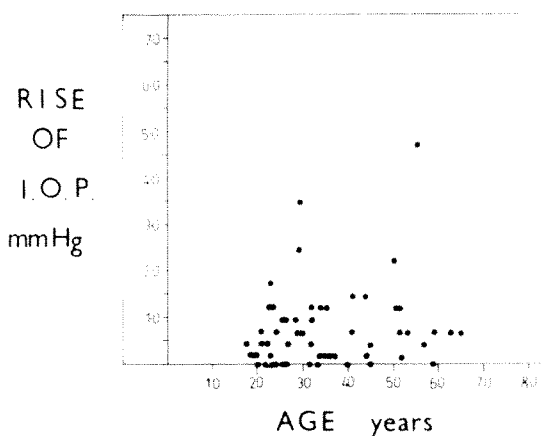


Fig. 1 Rise of intraocular pressure on lying—57 normotensive subjects.

(4) The pattern of the rise of intraocular pressure associated with change of position was different in the 2 groups. In the control group the mean rise, when measured at 0 min, was significantly higher than the mean rise measured at 15 min, 1.02 mmHg compared to 0.60 mmHg ($P < 0.05$). In the hypertensive group the mean rise at 15 min was significantly higher than that occurring at 0 min, that is, 1.21 mmHg compared to 0.61 mmHg ($P < 0.0005$). (5) When the control was compared with the hyper-

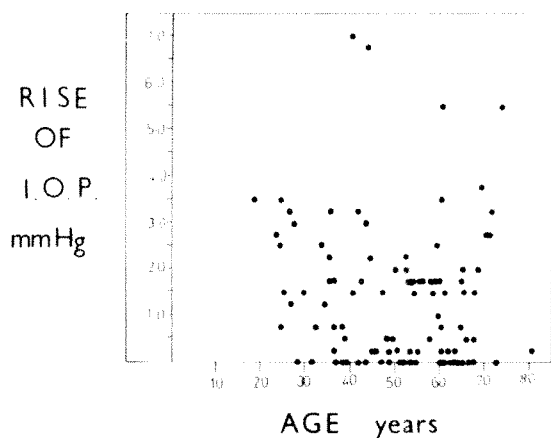


Fig. 2 Rise of intraocular pressure on lying—95 hypertensive patients.

Table 1 Intraocular and systemic blood pressure changes associated with change of posture

Position	Blood pressure	Intraocular pressure (mmHg)		
		Right eye	Left eye	Mean R + L eyes
<i>Controls</i>				
Sitting	114.7 ± 11.5 74.3 ± 8.3	13.9 ± 2.5	14.1 ± 2.8	14.0 ± 2.6
Lying at 0 min		14.8 ± 2.8	14.7 ± 2.9	14.7 ± 2.8
Lying at 15 min	111.4 ± 9.6 67.4 ± 9.6	14.6 ± 2.9	14.6 ± 2.9	14.6 ± 2.8
Rise at 0 min				1.0 ± 1.4
Rise at 15 min				0.6 ± 1.3
<i>Hypertensives</i>				
Sitting	147.8 ± 24.1 98.8 ± 12.8	14.0 ± 2.5	13.9 ± 2.6	13.9 ± 2.4
Lying at 0 min		14.4 ± 2.9	14.6 ± 3.1	14.5 ± 2.8
Lying at 15 min	147.4 ± 22.2 94.0 ± 14.9	15.1 ± 3.1	15.2 ± 3.1	15.1 ± 2.9
Rise at 0 min				0.6 ± 1.4
Rise at 15 min				1.2 ± 1.6

tensive group, the difference in the rise of pressure occurring at 0 min was not significant ($P \approx 0.07$), while the difference occurring at 15 min was significant ($P < 0.005$). This difference was tested after exclusion of hypertensive subjects who were not matched for age with control subjects, and the difference found was again significant ($P < 0.05$). It therefore appeared that this difference was not dependent upon age.

(6) In the control group the value for the rise of pressure occurring at 15 min was in extremely good agreement with that found for the similar group of control subjects in our original experiments, namely, 0.6 ± 0.8 mmHg (original group) and 0.6 ± 1.3 mmHg in the present study.¹

SYSTEMIC ARTERIAL PRESSURE (FIG. 1)

Within each group there was no significant difference between the mean arterial pressures measured with the patient in the sitting and lying position. The mean arterial pressure was significantly higher in the hypertensive group, measured in both the sitting and lying positions respectively ($P < 0.0005$ and $P < 0.0005$ respectively).

We found no correlation between individual changes of systemic pressure (whether of magnitude or direction) and the magnitude of the rise in the intraocular pressure in association with the change from sitting to lying. This confirms our previous findings.¹

DRUGS

We found no special relationship between any of the drugs taken by our subjects (including tobacco and alcohol) and the magnitude of the mean rise or intraocular pressure occurring with change of position.

MEDICAL HISTORY AND FAMILY HISTORY

Our results have not indicated any significant association of disease in the subjects or their relatives with the magnitude of the rise of intraocular pressure on change of position. However, this analysis was not deep and the numbers are too small for firm conclusions to be drawn.

FUNDUSCOPY

A detailed analysis of the relationship between the state of the disc, veins, arteries, and arteriovenous crossings of both eyes of all our subjects was performed. We failed to find a significant association between the mean rise of pressure at 0 min or 15 min and abnormality of any 1 of the above retinal variables within the hypertensive group. However, the presence of abnormal arteriovenous crossings was associated with a lower mean rise of

pressure at 0 min than that found in their absence, and the correlation approached significance ($2P=0.059$). Conversely the mean values at 15 min were very similar in the presence or absence of this abnormality.

Conclusions

Our results have shown that a group of hypertensive patients as a whole behaved differently from a group of normotensive, healthy subjects with respect to control of intraocular pressure. With a change of posture from sitting to lying the hypertensive patients showed a significantly higher mean rise of intraocular pressure after 15 minutes in the lying position. In this respect their behaviour resembles that of patients who have suffered a unilateral obstruction of a central or tributary retinal vein. In the latter group, therefore, such a rise of pressure at 15 min cannot be the result of retinal vein obstruction, but must be due to factors which are in operation before obstruction occurs.

The greater rise of pressure at 0 min in the normal subjects did not achieve significance but did show a trend which is interesting and worthy of further study, particularly as the rise of pressure occurring in glaucomatous eyes has been recorded as soon as the subject lies down, or at 2 minutes.⁵

Reference to Figs. 1 and 2 shows that while the mean rise of pressure of hypertensive patients as a group may be higher than that of normotensive subjects, all hypertensive patients do not behave in a similar way. In 41% the rise of pressure was less than 1.9 mmHg (mean + SD). Further, those who showed rises greater than this did not appear to fall into any particular age group: rises greater than the mean + SD occurred in patients as young as 18 years and as old as 70 years. This would suggest that the abnormal rise in pressure is not the result of the hypertensive process at work over a period of time but rather an anomaly which predates it in some hypertensives. If this is so, we may be dealing with an abnormality which, being present in only some subjects, is of importance as an indication of those hypertensive patients likely to suffer a retinal vein obstruction.

Addendum

The belief that the abnormal intraocular pressure response is the result of underlying anomaly shown by patients who develop hypertension and glaucoma led us to investigate a small number of diabetic patients, since there is a considerable amount of clinical evidence to link hypertension, diabetes, and

primary open-angle glaucoma. Thus, this type of glaucoma is more common in the diabetic than in the nondiabetic population, and diabetes is more often found in patients with an open-angle glaucoma than is the case in the general population.⁶ Both diabetes and open-angle glaucoma can be provoked or exacerbated by the administration of glucocorticosteroids, and both groups of patients show abnormally high rises of intraocular pressure in response to the administration of topical steroids.⁷

Diabetics and hypertensives share the misfortune of vascular retinopathies, which have many features in common, including the development of venous obstruction, a complication which is not uncommonly associated with open-angle glaucoma, and, finally, in all these disorders we find strong evidence of the influence of inherited factors in their genesis.⁸⁻¹⁰

Patients and methods

We examined 14 patients of whom 4 were men and 10 women. Their ages ranged between 25 and 70 years with a mean value of 53.36 ± 13.3 years. All patients had shown glycosuria together with random blood sugar levels >12.0 mmol/litre at some time, and we found that the duration of their disease varied between 4 and 30 years (in those cases where this could be established with reasonable certainty). All except 2 patients had presented with acute symptoms, the remaining 2 having disease of the maturity onset variety. According to our criteria (see above) 8 patients had a systemic hypertension, while 6 were normotensive, 11 had retinopathy associated with their diabetes, and 1 normotensive patient had unilateral retinal vein obstruction. All the patients except 4 were receiving oral therapy for their diabetes, the drugs used being chlorpropamide and glibenclamide. One patient was controlled by diet only, and 3 were being treated by combinations of soluble and long-acting insulin preparations. The hypertensive patients requiring therapy were being treated with various hypotensive agents, including methyldopa, debrisoquine, propranolol, hydralazine, and the thiazide diuretics. One patient was receiving treatment with thyroxine.

We carried out intraocular pressure measurements on this group using the same protocol as was used in our pilot study of 12 hypertensive patients.

Results

The mean rise of intraocular pressure after the subjects lay down was 4.9 ± 1.8 mmHg. This value is clearly significantly greater than that found in our control group (see above, 0.6 ± 1.3 mmHg), being

Table 2 Mean rises of intraocular pressure in 2 subgroups of diabetic patients

Subgroup 1				Subgroup 2			
Patient	Sex	Age	Mean rise IOP (mmHg)	Patient	Sex	Age	Mean rise IOP (mmHg)
1	F	25	7.0	8	F	66	8.0
2	F	33	6.0	9	F	54	6.0
3	F	50	4.5	10	F	65	2.5
4	F	47	3.0	11	F	65	5.2
5	M	45	3.0	12	M	60	6.0
6	M	50	3.2	13	F	70	3.2
7	M	52	7.5	14	F	65	3.5
Mean		43.2 $\pm$ 10.2	4.9 $\pm$ 1.9			63.6 $\pm$ 5.1	4.9 $\pm$ 1.9

somewhat greater than the value found for our pilot study of 12 hypertensives (see above, 3.5 ± 2.5 mmHg). This study of a small group of diabetics therefore suggests very strongly that an inability to control the level of intraocular pressure with change of posture (from sitting to lying) is present in diabetics as well as hypertensives. Furthermore, it would seem that this abnormality is not determined by the presence of the coexisting systemic hypertension in 8 of our patients, since an analysis of the group has shown that the mean rise of intraocular pressure by the 6 normotensive diabetics was 4.7 ± 1.8 mmHg, while that shown by the 8 hypertensive patients was 5.0 ± 2 mmHg, and these figures are not significantly different.

It will be noted that the average age of the 3 groups of patients we have studied is 34.5 years for the control subjects, 49.3 years for patients with hypertension, and 53.3 years for patients with diabetes mellitus. However, we do not believe that the abnormal rises of intraocular pressure associated with change of posture seen in our hypertensive and diabetic subjects are dependent on this age difference for the following reasons.

(1) Within the hypertensive group patients showing rises of intraocular pressure greater than 1.9 mmHg (mean + SD for control subjects) when measured at 15 minutes did not fall into any particular age group, such rises occurring in patients as young as 18 years and as old as 70 years (see above and Figs. 1 and 2).

(2) The mean difference in the rise of intraocular pressure occurring in the control and hypertensive groups was tested statistically to establish whether the greater rise shown by the latter group was related to the fact that the average age of these patients was higher than that of the control subjects. Comparison of the mean rises of pressure in age-matched sub-

jects from these 2 groups again proved to be statistically significant ($P < 0.05$) (see above, Result 5 of Main Study).

(3) The diabetic group tested was relatively small but the age range was considerable, i.e., from 25 years to 70 years. As with the hypertensive patients high rises of intraocular pressure occurred in subjects at both ends of the age scale. Thus in our 2 youngest diabetic patients, aged 25 and 33 years, the rises of intraocular pressure were 7.0 and 6.0 mmHg respectively, while 2 of our older patients aged 66 and 60 years had rises of 8.0 and 6.0 mmHg.

To test the significance of the age factor in this small number of subjects we divided our 14 diabetic patients into 2 groups such that the first group contained the 7 youngest and the second group the 7 oldest patients. Comparison of the mean rises of intraocular pressure found in the 2 groups showed no significant difference despite the difference in mean ages; that is, the mean rise found was 4.9 ± 1.9 mmHg in the younger group and 4.9 ± 1.9 mmHg in the older group, though the mean ages were 43.2 ± 10.2 and 63.6 ± 5.1 years respectively (see Table 2).

We therefore believe that this abnormality is not age-related and may be the measurement of a fundamental defect linking hypertension, diabetes mellitus, and primary open-angle glaucoma.

We gratefully acknowledge the support by the Wolfson Foundation and thank the staff of the Wellcome Research Laboratories, Beckenham, where a great deal of this study was carried out. Their very valuable co-operation was much appreciated.

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Colour vision in patients with chronic simple glaucoma and ocular hypertension

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SUMMARY Normal subjects and patients with chronic simple glaucoma and ocular hypertension were examined with the Farnsworth-Munsell 100 hue test. Two groups of glaucoma patients were studied, one group having field defects in both eyes and the other being 'unilateral' in the sense that one eye had a full visual field. The stage of the disease was assessed by the amount of field loss or by the amount of optic disc damage as expressed by the vertical cup:disc ratio. Hue discrimination in eyes with glaucomatous field defects was worse than in eyes of normal subjects, but there was no clear indication of one range of colours being more affected than another. In glaucoma patients with field defects in both eyes the difference in error scores between the 2 eyes was greater than in normal subjects. There was a significant correlation between the degree of impairment of hue discrimination, expressed as the error score, and the amount of glaucomatous field loss. There was also a significant correlation between error score and the amount of glaucomatous damage to the optic disc, expressed by the vertical cup:disc ratio. Findings in a group of patients with ocular hypertension suggested that some of these were cases of incipient glaucoma.

Defective colour vision has been established as part of the impairment of visual function in eyes affected by chronic simple glaucoma.¹⁻⁵ The main purpose of the investigation reported in this paper was to study the relationship of the degree of loss of hue discrimination to the stage of glaucoma, the latter being assessed not only in terms of visual field loss, but also in relation to optic disc damage expressed quantitatively as the vertical cup:disc ratio. Hue discrimination tests were carried out on patients with chronic simple glaucoma, some of whom had visual field defects in both eyes and some in one eye only. Some cases of ocular hypertension were included in this study, because it was highly probable that among them would be a proportion of individuals with incipient chronic simple glaucoma.

Patients and methods

The patients tested were attending the Glaucoma Clinic of the Institute of Ophthalmology and Moorfields Eye Hospital for routine diagnosis and management. All had shown intraocular pressures of more

than 21 mmHg with open angles. Those classified as chronic simple glaucoma had typical glaucomatous visual field defects in one or both eyes; if both fields were full, the patient was regarded as having ocular hypertension. A small number of normal volunteers, mostly relatives and friends accompanying patients, were also tested.

In some patients the Farnsworth Munsell 100 hue test was conducted in the usual way, while in others a modified procedure was used as follows. A wheel 26 in (66 cm) in diameter was fixed to a pivot mounted on an inclined base so as to be capable of rotation through 360° (Fig. 1). Around its perimeter the wheel carried 89 nylon pegs measuring $\frac{3}{4}$ in (1.9 cm) in height and shaped to take the standard Farnsworth test caps. Four reference caps were permanently fixed to the wheel corresponding to the first reference cap on each of the Farnsworth 100 hue boxes; they were placed between the pegs of caps nos. 85 and 1, 21 and 22, 42 and 43, and 63 and 64 respectively. The 85 caps were kept on pegs fixed to the base of a tray below the wheel. Illumination was provided by 2 daylight fluorescent tubes fixed on each side of the wheel and enclosed in a metal reflector so that the light was evenly projected on to the wheel and tray. The luminance was around

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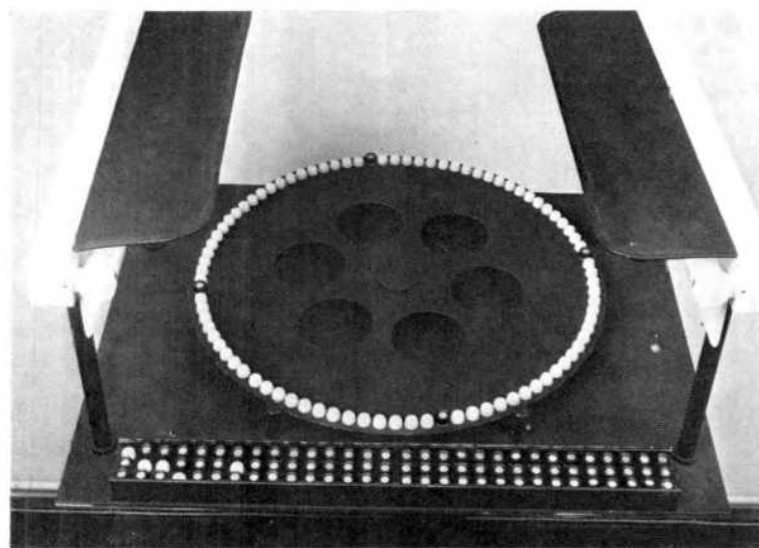


Fig. 1 Farnsworth-Munsell 100 hue colour vision test using the 'wheel' with nylon pegs mounted on an inclined base and fixed to a pivot and the Farnsworth-Munsell 100 hue caps kept on pegs fixed to a base illuminated by 2 daylight fluorescent tubes.

107 lux. The procedure was the same for the conventional Farnsworth-Munsell 100 hue test except that, instead of presenting the caps in 4 separate boxes, the caps were placed in a random fashion on the tray. The patient sat facing the wheel and was briefed with the details of the test. With one eye covered and wearing his near correction, if any, the patient was required to arrange the caps in the right order starting from the reference cap between peg 85 and 1. When all caps had been fixed to the pegs on the wheel the positions of the caps were checked and marked on a special chart. The same procedure was repeated for the second eye.

A computer programme was developed to score and plot the results on a CIL model 7341 incremental plotter. The programme to produce the plots was written in Fortran and was run on an IBM 360/65 computer. The raw data, that is the patient's response for each cap, were stored on magnetic discs having been put there by means of a visual display unit connected to the computer. Before any scores were calculated or any plotting took place the data were checked by means of a programme which indicated any data points greater than 85 or appearing twice and which also pointed out any missing cap number. When the data were free from error, the plotting programme was run. This programme also calculated the score at each cap, the total score, and the average and percentage error for each box and for the four boxes combined, this information being given in a table above the graph. The plot was obtained by converting the scores into (x y) co-ordinates and joining adjacent points. If the score at a particular cap was greater

than 16, it was not plotted in the normal way, since it would have meant drawing lines outside the chart. Instead, the score was written on the periphery of the chart and no lines were drawn to the adjacent points. The plot of the graph and table took about 10 minutes.

Paired *t* tests comparing the mean difference in the scores of the standard 100 hue test and the 'wheel method' were carried out, and it was concluded that there was no systematic change in the scores with the wheel as compared with the standard test.

Cup:disc ratios were obtained from measurements of optic disc photographs as previously described.^{6,7}

The visual fields were examined on a Goldmann perimeter by static presentation of the 1:4 stimulus in 188 different positions within the central 25°. The extent of field loss was expressed as the number of stimuli not seen.

Results

ERROR SCORES

Table 1 summarises the average error scores for the 100 hue tests for normal subjects, glaucoma patients, and patients with ocular hypertension. The groups were matched for age and sex, and each group comprises results for 26 eyes. The average age throughout was 57 years. The glaucoma patients in Table 1 were 'unilateral' cases as regards field defects; that is to say, an intraocular pressure above 21 mmHg had been found with open angles in both eyes, but in only one eye had a typical glaucomatous

Table 1 *Average error scores for normal subjects and for patients with 'unilateral' chronic simple glaucoma and ocular hypertension*

	Average age (years)	Average error scores				Total
		Box 1 Red to yellow	Box 2 Yellow to blue-green	Box 3 Blue-green to blue	Box 4 Blue through purple to red	
Normal subjects	57.4					
26 eyes		13.7	16.1	16.7	17.1	63.7
Glaucoma patients	57.1					
26 eyes with field defects		37.2	49.5	50.3	43.8	180.7
26 eyes with full fields		16.8	20.3	19.0	20.8	76.9
Ocular hypertension	57.0					
26 eyes		15.0	23.6	22.7	20.1	81.3

Table 2 *Interocular differences in error scores on 100 hue test*

	No. of individuals	Mean differences in error scores				Total
		Box 1 Red to yellow	Box 2 Yellow to blue-green	Box 3 Blue-green to blue	Box 4 Blue through purple to red	
Normal subjects	24	4.2	4.8	8.8	8.3	20.0
Glaucoma patients with field defects in both eyes	16	24.5	22.8	29.7	33.1	96.9
Patients with ocular hypertension	30	14.3	14.2	18.8	12.8	45.6

field defect been demonstrated on the Goldmann perimeter. The details of the optic discs, visual fields, and Farnsworth-Munsell 100 hue tests of a typical patient from this group are shown in Figs. 2a, b, c, and 3a, b, c.

Table 2 gives the mean differences in scores between the 2 eyes of normal subjects, patients with 'bilateral' chronic simple glaucoma (i.e., with field defects in both eyes—a completely separate group from those in Table 1) and patients with ocular hypertension. The normal subjects and patients with ocular hypertension included those in Table 1.

The error scores were analysed statistically from 3 aspects: (a) comparison between the 4 boxes of the 100 hue test; (b) comparison between the various groups of patients and subjects; (c) using differences in scores between the 2 eyes.

(a) Statistical analysis showed some significant differences between the scores for the various boxes, but there was no consistent pattern when the scores for all groups of eyes were considered.

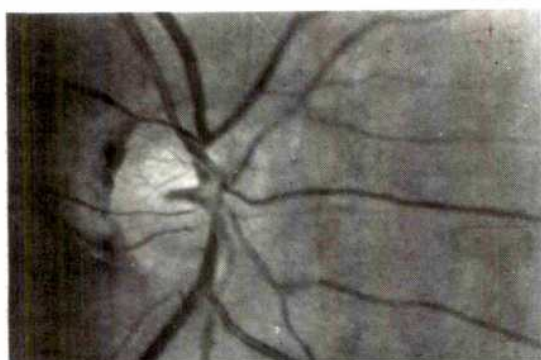
(b) When the error scores for the various groups of eyes were considered, it was clear that the scores for eyes with glaucomatous field defects were

higher than those for eyes in the other 3 groups ($P < 0.001$), and this was so for all 4 boxes and for total scores. Otherwise no differences at the 5% level or less were found between the various groups of eyes.

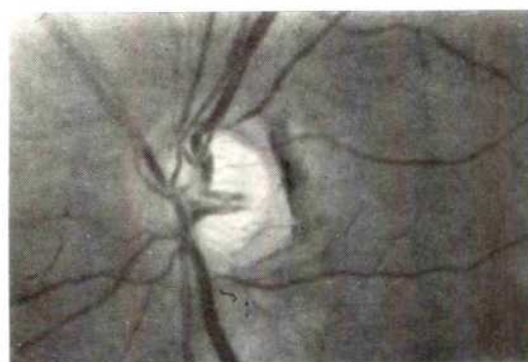
(c) When differences in error scores between the 2 eyes of individual patients were analysed, those with bilateral glaucomatous field defects had significantly higher scores than normal subjects ($P < 0.01$). The glaucoma patients also differed from those with ocular hypertension except in the third box (blue-green to blue). Patients with ocular hypertension were significantly different from normal subjects only in the first and second boxes (red to yellow and yellow to blue-green).

CORRELATIONS BETWEEN 100 HUE ERROR SCORES AND CUP:DISC RATIOS

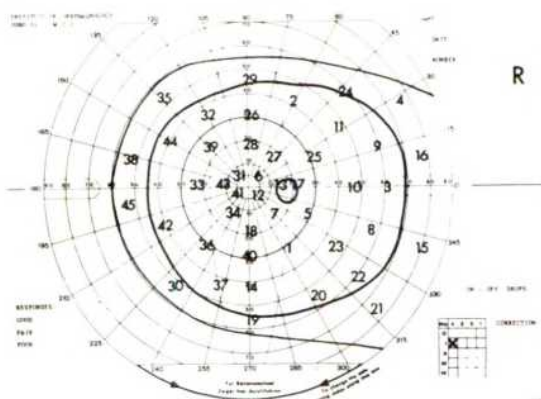
Correlation between error score and amount of visual field loss. For the 26 glaucomatous eyes with field defects in Table 1 a highly significant correlation was found between the error score and the number of stimuli not seen in the visual field test ($r = 0.61$, $P < 0.001$). There was no correlation between the



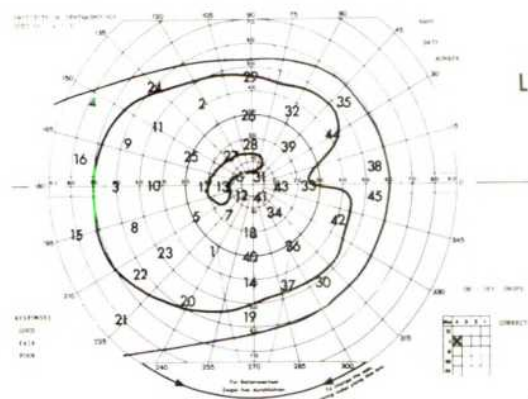
2a



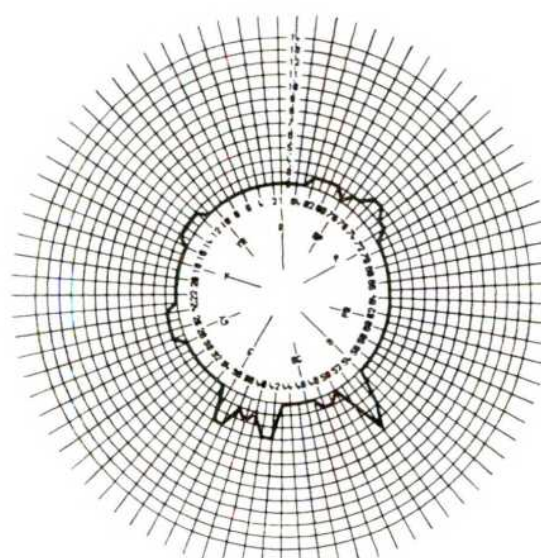
3a



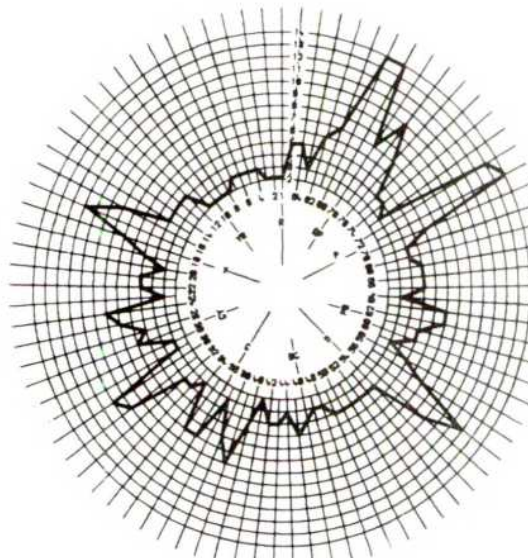
2b



3b



2c



3c

Figs. 2a, b, c (right eye) and 3a, b, c (left eye) Details of the optic discs (cup:disc ratio—right eye 0.55 and left eye 0.8), visual fields and Farnsworth-Munsell 100 hue colour vision tests of a 57-year-old male patient with chronic simple glaucoma, showing unilateral field defect (corrected visual acuity right eye 6/5 and left eye 6/4—pupils 4 mm right and left eyes).

Table 3 Correlations between cup:disc ratios and 100 hue error scores in 'unilateral' chronic simple glaucoma

Eye	Box 1 Red to yellow	Box 2 Yellow to blue-green	Box 3 Blue-green to blue	Box 4 Blue through purple to red	Total
Right	**	0	***	0	**
Left	0	**	***	**	**
Right minus left	***	***	***	***	***
Eyes with full fields	0	0	0	0	0
Eyes with field defects	0	0	*	**	*

0 = No significant correlation, *0.05 > P > 0.01, **0.01 > P > 0.001, ***0.001 > P.

error score and the closeness of the field defect to fixation.

Correlation between error score and cup:disc ratio. The following correlations were computed: (1) between the right cup:disc ratio (CDR) and the right score; (2) between the left CDR and the left score; (3) between (right CDR minus left CDR) and (right score minus left score); (4) between CDR in eye with full field and score in eye with full field; (5) between CDR in eye with field defect and score in eye with field defect; (6) between (CDR in eye with field defect minus CDR in eye with full field) and (score in eye with field defect minus score in eye with full field).

These findings are summarised in Table 3, from which it can be seen that, when eyes with field defects were involved, some degree of correlation between CDR and score could be demonstrated, at varying levels of significance and usually not for the complete range of hues. Interocular differences in CDR and score gave the more significant correlations. In eyes with full fields no significant correlations between CDR and score were found.

In 24 patients with ocular hypertension a significant ($P < 0.01$) correlation was found between the interocular differences in CDR and the interocular differences in 100 hue score.

Discussion

The results show clearly that hue discrimination is well below normal in eyes with established chronic simple glaucoma, that is, when field defects are present. The finding of error scores above normal in eyes with full fields in glaucomatous patients and in cases of ocular hypertension suggests that impairment of hue discrimination occurs in the relatively early stages of the disease. The highly significant correlation between error score and the amount of visual field loss already reported by Austin⁹ shows that in the later stages of the disease

reductions in hue discrimination and field deterioration take place together.

In glaucoma patients with field defects in both eyes the difference in error scores between the 2 eyes was greater than in normal subjects. This would appear to be a reflection of the difference in severity of glaucomatous damage frequently evident between the 2 eyes of individual patients. A similar result was obtained, though of smaller magnitude and limited to the first 2 boxes of the 100 hue test, in patients with ocular hypertension, suggesting that this group contained cases of incipient glaucoma.

The cup:disc ratio, measured from photographs of the optic disc, was used to provide an objective index of the stage of the disease. In glaucomatous patients with field defects in one eye only, the highly significant correlation which was found between the interocular differences of error score in the 100 hue test, and the interocular difference in cup:disc ratio strongly suggests that the degree of impairment of colour discrimination is related to the severity of glaucomatous damage to the optic discs. When the error scores and cup:disc ratios were analysed for the eyes with field defects, significant correlations between these parameters were again found, though not for the complete range of the 100 hue test; this finding also indicates that loss of colour discrimination is related to optic disc damage.

The finding of a correlation between cup:disc ratio and error score provides the possibility of extending the investigation to the stage of glaucoma in which a field defect has not been demonstrated. For example, the study can be extended to eyes with full fields in patients having established chronic simple glaucoma in the other eye, and to patients with ocular hypertension, some of whom can be presumed to be cases of incipient glaucoma. In the present investigation the results for these 2 groups, while not in disagreement, are not mutually supportive. No correlation was found between the magnitude of the cup:disc ratio and error scores in

eyes with full fields in 'unilateral' chronic simple glaucoma. On the other hand interocular differences in cup:disc ratios showed a significant correlation with interocular differences in error scores in 24 patients with ocular hypertension. In this respect, it should perhaps be remembered that in glaucoma patients the most significant correlations between cup:disc ratios and error scores were found when interocular differences were analysed (Table 3). From the clinical viewpoint the suspicion that a patient with 'ocular hypertension' should be regarded as having early chronic simple glaucoma would seem to be increased by finding an asymmetry of hue discrimination which matched asymmetries of cup:disc ratio and intraocular pressure.

We wish to thank Mr L. Yerlett for constructing the wheel system, Mr H. Donovan for developing the computer program, the Audio Visual Department, Institute of Ophthalmology for illustrations, and Mrs J. Kennedy for typing the manuscript.

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Interocular comparison of contrast sensitivities in glaucoma patients and suspects

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SUMMARY Glaucoma affected the ability to detect low-contrast, flickering patterns ('DRC' measurement). DRC patterns were foveally viewed, of low spatial frequency, and flickering at 8 hertz. Interocular comparisons were performed in control subjects, in ocular hypertensives, and in glaucoma patients with asymmetric damage. Interocular differences in DRC tended to be of greater magnitude in the glaucoma patients than in the ocular hypertensive patients or control subjects. In the glaucoma patients DRC was consistently lower in the eye with the greater field defect than in the other (more normal) eye. In patients with optic disc asymmetry DRC was lower in the eye with the more abnormal disc. Treatment asymmetries did not appear to play a significant role in these relationships. When examined by interocular comparisons DRC showed no consistent relationship to Snellen visual acuity or to level of intraocular pressure at the time of DRC testing.

The early stages of glaucomatous visual damage are generally detected outside of the central 5-10° of the visual field. As long as Snellen acuity remains good, it is ordinarily assumed that vision in the central field has not yet been affected by the disease process. However, we have found¹ abnormalities of central vision in glaucoma patients who had normal Snellen acuities. These abnormalities occurred in a variable named the 'dynamic response coefficient' or DRC, which is based on the contrast required for the detection of flickering patterns. Two types of stimuli, a homogeneous flickering field, and a counterphase flickering grating of low spatial frequency, were presented on a centrally fixated screen 4° of visual angle in diameter. The mean contrast sensitivity of these 2 stimuli (defined as the DRC) was consistently lower in glaucomatous than in normotensive eyes. Thus there appeared to be a relationship between central retinal performance, as measured by the DRC, and the more peripheral visual field defects detected by Goldmann kinetic perimetry.

Glaucomatous damage commonly occurs in one eye earlier than in the other. We examined *interocular* DRC differences in patients with asymmetrical

Table 1 *Subject groups*

Group*	Number of subjects	Age (years)	
		Mean	(SD)
(1) POAG	17	52	(18)
(2) OHT	19	46	(17)
(3) Control	16	52	(23)

*POAG = Primary open-angle glaucoma patients, OHT = Ocular hypertensive patients.

glaucoma in order to explore further the sensitivity and specificity of this new test of foveal vision in glaucoma.

Materials and methods

SUBJECTS

Three groups were studied. These were: (1) 17 patients with primary open-angle glaucoma (POAG) chosen for asymmetric damage to visual fields and optic discs; (2) 19 ocular hypertensive (OHT) patients; and (3) 16 control subjects (Table 1). The mean ages of the control and POAG groups were 52 years and of the OHT group was 46 years. The patient groups were defined by the same selection criteria used in our previous report¹ and included some of those patients. Patients and control subjects

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with ocular pathology other than glaucoma, or with any neurological disorder, were excluded from the study. In all cases Snellen visual acuities were 6/12 or better, and all except 2 of the total of 104 eyes had acuities of 6/9 or better.

Each of the glaucoma patients and ocular hypertensives had had intraocular pressure (IOP) readings of 22 mmHg or higher on 2 or more occasions. Goldmann dynamic perimetry showed normal fields bilaterally in the OHT group. In the POAG group the glaucomatous defect was restricted to one eye in 13 patients. The other 4 had field defects in both eyes, more severe in one than in the other. Six of the 13 POAG patients with unocular visual field damage had only mild defects. These were: constriction of the central field in 3 eyes; an early, relative paracentral scotoma in 2 eyes; and a superior nasal depression in one eye. The other 7 patients had more severe defects. These were: nasal step with central constriction in one eye; Bjerrum scotoma with central constriction in 3 eyes; Bjerrum scotoma with paracentral scotoma and nasal defect in one eye; and sector defect in one eye. Of the 4 patients with visual field damage in both eyes 1 showed only mild defects, consisting of central constrictions, more severe for one eye than for the other. The others showed, in addition to enlarged blind spots, paracentral scotoma (1 eye), Bjerrum scotoma (4 eyes), peripheral nasal step (1 eye), and nasal constriction (2 eyes).

PSYCHOPHYSICAL TESTING

The stimulus was presented to central vision on an oscilloscope screen that subtended 4° of visual angle.¹ The mean luminance of the screen remained constant throughout each test session. The mean luminance level was 6 foot-lamberts (20.6 cd/m^2) for 2 of the control subjects, and for 10 of the OHT and 4 of the POAG patients; for the rest the level was 40 foot-lamberts (137 cd/m^2). As this difference had no apparent effect on results of the interocular comparisons, it will not be referred to again in this report.

The psychophysical testing method has been described previously.¹ The DRC test employs 2 stimulus conditions: 'diffuse flicker' and 'counterphase flicker'. In the diffuse flicker condition the subject viewed a blank, evenly illuminated screen. Its luminance changed abruptly back and forth between 2 levels at a rate of 8 hertz. In the counterphase flicker condition the stimulus was a grating pattern of dark and light bars with a sinusoidal luminance profile and a spatial frequency of 1.2 cycles per degree. That is, the 4-degree stimulus-field contained 5 cycles of the sinusoidal grating pattern, which means there were 5 dark bars and 5 light bars

on the screen at a given moment. This is a relatively coarse grating. It was temporally modulated at a rate of 8 hertz: 16 times per second the pattern reversed, i.e., each dark bar changed abruptly into a bright one, and vice versa.

While mean luminance remained constant during each test, contrast was varied. Contrast is defined as the ratio of the difference between peak and mean luminance of the test screen to its mean luminance, or equivalently, as $(L_{\text{max}} - L_{\text{min}})/(L_{\text{max}} + L_{\text{min}})$, where L_{max} is the highest level of luminance in the test pattern, and L_{min} is the lowest.

The contrast thresholds of each subject were measured both for the diffuse flickering field and for the counterphase grating, as will be described, and used to derive the corresponding contrast sensitivities.

Contrast thresholds were determined by a method of 'constant stimuli'. The flickering stimulus was presented at a given contrast level for a duration of 4–6 seconds and the subject was asked whether or not he saw the pattern (flicker or grating). Then the contrast was changed and the stimulus was presented again. Between presentations the subject looked at a blank screen with luminance matched to that of the test screen. Each contrast change was made at random, either upwards or downwards, and by an increment of 2 decibels (db) or some multiple of 2 db. The first few presentations were used to bracket the threshold, and the subsequent presentations were restricted to a 10 db interval containing the threshold. In general, 4 independent replications were performed at each of the discrete contrast levels within this interval. The contrast threshold for diffuse flicker was the minimum contrast at which the subject detected the flicker on about half of the presentations. The reciprocal of this threshold was the contrast sensitivity to diffuse flicker. The contrast threshold for the counterphase flickering grating was the minimum contrast at which the subject detected the bar pattern on about half the presentations, and the grating contrast sensitivity was the reciprocal of this latter contrast threshold. Each such sensitivity determination took about 4–5 minutes.

The average of the diffuse flicker contrast sensitivity and the counterphase grating contrast sensitivity has been named 'dynamic response coefficient' or DRC.¹ The DRC may be viewed as a crude estimate, obtained at a temporal modulation frequency of 8 hertz, of the low spatial frequency end of the foveal contrast sensitivity curve. DRC was measured on a logarithmic scale in decibels. If the DRCs of the 2 eyes differ by 6 db, then the contrasts required by one eye are double those required by the other.

Results

In the glaucoma patients with asymmetric visual field damage DRC differences between the right and left eye tended to be larger than in the ocular hypertensives or the control subjects (Fig. 1). Although many from the latter 2 groups had interocular DRC differences as large as 2 db, only 1 from each had a difference as large as 3 db. None of the control or OHT interocular differences was as large as 4 db, but more than half the POAG interocular differences were of this magnitude or larger ($P < 0.01$, chi square).

The direction of the DRC asymmetry was then examined in relation to the direction of asymmetry of 4 other variables: field loss (Fig. 2, 1st column); optic disc morphology (2nd column); visual acuity (3rd column); and intraocular pressure (IOP) (4th column). In the patients with unilateral visual field loss the direction of field-loss asymmetry was obvious. In patients with visual field losses in both eyes the criteria were as follows. It was assumed that the eye with the more constricted field, and/or with more and/or larger scotomata, and/or with scotomata that more closely encroached upon the foveal part of the field, is the one with the greater visual field damage. Further, one eye was considered more abnormal than the other with respect to optic disc morphology (2nd column) if its cup/disc ratio was greater than the other eye's by 0.2 or more, with respect to visual acuity (3rd column) if its

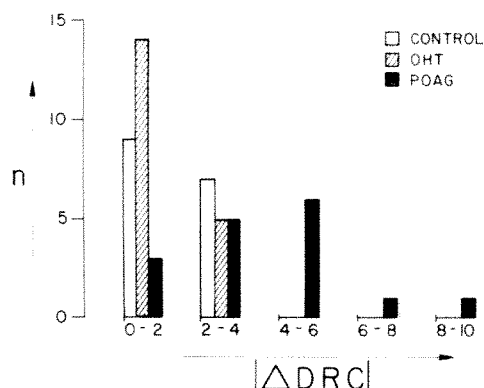


Fig. 1 Size distributions of interocular DRC differences for each group. Height of each bar signifies the number of patients or control subjects (see key) having an interocular difference within the range specified beneath it ('2-4' means '2 or more but less than 4'). DRC signifies dynamic response coefficient (see text). $|\Delta DRC| = |DRC(OD) - DRC(OS)|$ is the absolute value of the difference between DRC of right eye and DRC of left eye. OHT signifies ocular hypertensive patients; POAG, primary open-angle glaucoma patients.

Snellen acuity ratio was less than the other eye's by 0.2 or more, and with respect to intraocular pressure (last column) if its applanation tension exceeded the other eye's by 2 mmHg or more.

In Fig. 2 the ordinate, ΔDRC , signifies the amount by which DRC of the eye showing greater abnormality in one of these other variables deviates from DRC of the fellow eye, that is, $\Delta DRC = (DRC \text{ of more abnormal eye}) - (DRC \text{ of fellow eye})$. In the glaucoma patients DRC was lower in the eye with the greater glaucomatous visual field damage. The consistently negative values of ΔDRC in the first column of Fig. 2 signify that the eye with more field

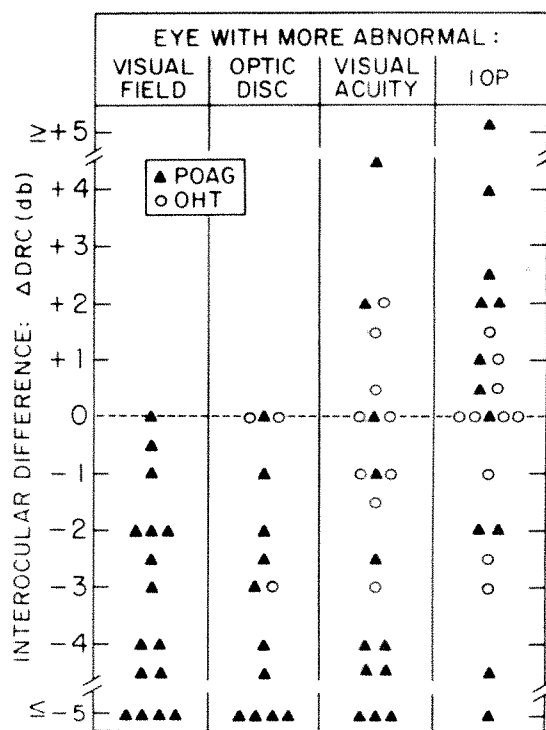


Fig. 2 Relations of DRC interocular differences to interocular differences in 4 other variables. Filled triangles represent interocular differences of primary open-angle glaucoma (POAG) patients, open circles of ocular hypertensive (OHT) patients. The ordinate, ΔDRC , is interocular difference of DRC in db. DRC is defined in the text. A difference of 6 db would mean that the mean contrast sensitivity to 8 Hz flicker of one eye was twice that of the other. In each column a point below zero (negative ΔDRC) signifies that the eye with the greater defect of the type specified at the top of that column had a lower DRC than the other eye; a point above zero (positive ΔDRC), on the other hand, signifies that the eye showing more of the specified defect had a higher DRC than the other. See text for additional explanation.

loss nearly always had a DRC level less than its fellow eye ($P < 0.001$ by sign test). The eye with the more abnormal optic disc was similarly compared to its fellow eye (Fig. 2, second column); the DRC was never higher and was usually lower in the eye with the more abnormal optic nerve head ($P < 0.001$ by sign test).

The relations of DRC to 2 other variables were examined in the same way. Interocular DRC differences were not significantly associated with interocular differences in Snellen visual acuity. The eye with poorer Snellen acuity might have a DRC either higher or lower than its fellow eye. This is shown in the third column of Fig. 2, where Δ DRC is in some instances above and in others below zero. Similarly, the IOP measured at the time of the DRC test does not appear to be a main determinant of DRC, since the DRC of the eye with the higher pressure was in some instances above and in others below that of the fellow eye (Fig. 2, fourth column).

The observed pattern of interocular differences in DRC could not be accounted for by pharmacological effects at the time of testing. Of the 17 POAG patients the majority were receiving either no glaucoma medication (7 patients) or the same medication in both eyes (5 patients). There were only 5 instances in which one eye was receiving drug therapy different from the other. Three were unilateral POAG patients who used epinephrine drops in the eye with the glaucomatous visual field damage (their Δ DRC magnitudes were 4.0, 4.5, and 5.5 db). The remaining 2 were unilateral POAG patients who used multiple medications, with pilocarpine only in the eye *without* visual field damage (Δ DRC magnitudes were 2 and 15 db); for these 2 patients the visually more normal but pilocarpine-medicated eye had a smaller pupil and lower retinal illumination than the glaucomatous eye. Nevertheless, in these as in all except 1 of the other POAG patients DRC was lower in the eye with greater glaucomatous visual field damage.

Discussion

Interocular DRC disparities ($|\Delta$ DRC|) tended to be larger in the asymmetric POAG patients than in control subjects. Interocular disparities are common in POAG, and increased magnitudes of asymmetry are sometimes clues to pathology. Interocular differences in IOP are often abnormally large in glaucoma patients.² In diagnosing glaucoma, optic disc asymmetry^{2,3-6} or afferent asymmetry of pupillary response⁷ may be significant even in the absence of definite glaucomatous defects. It may be that DRC asymmetry can be included as another such diagnostic sign of POAG. It remains to be

seen whether abnormally large interocular DRC disparities will occur in glaucoma patients who do not otherwise manifest clinical asymmetry.

The interocular DRC differences of OHT patients were indistinguishable from those of control subjects (Fig. 1). This suggests that imminent POAG in OHT patients may not be signalled by increased magnitudes of DRC asymmetry. Or else one could assume that none of the ocular hypertensive patients we tested will develop glaucoma. At this point we have no evidence that interocular DRC differences will have predictive value. Only long-term follow up of OHT patients can provide such evidence. Further, even if DRC asymmetry sometimes warns of impending asymmetric glaucomatous damage, continued DRC *symmetry* will not be reassuring, since early glaucomatous damage may occur symmetrically.

Our most important finding has to do with the directions rather than the magnitudes of interocular differences. Apparently there is a specific association of DRC depression with glaucomatous visual field and optic nerve head defects. A similar association had already been demonstrated in a different manner by intergroup comparisons of POAG patients with control subjects.¹ Because the observed DRC interocular differences do not seem to depend on the IOP differences prevailing at the time the DRC test is performed, we infer that (within the observed range of IOPs) DRC depression probably reflects the chronic more strongly than the acute effects of raised IOP.

Further, both our previous report and this one provide evidence that the DRC losses in the glaucoma patients are not attributable simply to aging. Age does affect contrast sensitivity, and aging is associated with a contrast sensitivity loss at low spatial frequencies. This was reported by Atkin and his colleagues¹ and established recently by Sekuler and collaborators.⁸ The loss in glaucoma, however, exceeds the loss due simply to age by a factor of 3, as was shown by comparing contrast sensitivity at low spatial frequencies in glaucoma patients and age-matched controls.¹ Clearly the present finding of a *within-subject* interocular association between glaucomatous changes and DRC loss provide another demonstration of this specificity of the DRC test.

The association of DRC depression with changes in the optic nerve head and visual field in patients without loss of acuity or other evidence of foveal dysfunction means that early glaucoma affects foveal as well as peripheral vision. Apparently these foveal changes in glaucoma can be detected by DRC when they are not detected by kinetic perimetry or by Snellen visual acuity measurements. Still, we are

far from sure that this procedure will prove to be the most sensitive and specific psychophysical technique for detecting early foveal changes in glaucoma. The DRC test measures the detectability of coarse targets flickering at 8 hertz. Tyler⁹ recently reported that many patients with glaucoma have not only peripheral but also foveal contrast sensitivity losses to flickering targets. He confirmed the magnitude of the losses in glaucoma that we had reported¹ at a flicker rate of 8 hertz. However, he also found that losses commonly occur at temporal frequencies substantially above 8 Hz, and their magnitudes appear to be greater at the higher temporal frequencies. It remains to be seen whether contrast sensitivity studies that include a range of temporal frequencies above 8 Hz can generate a test of greater clinical usefulness than the 8 Hz test we have been employing.

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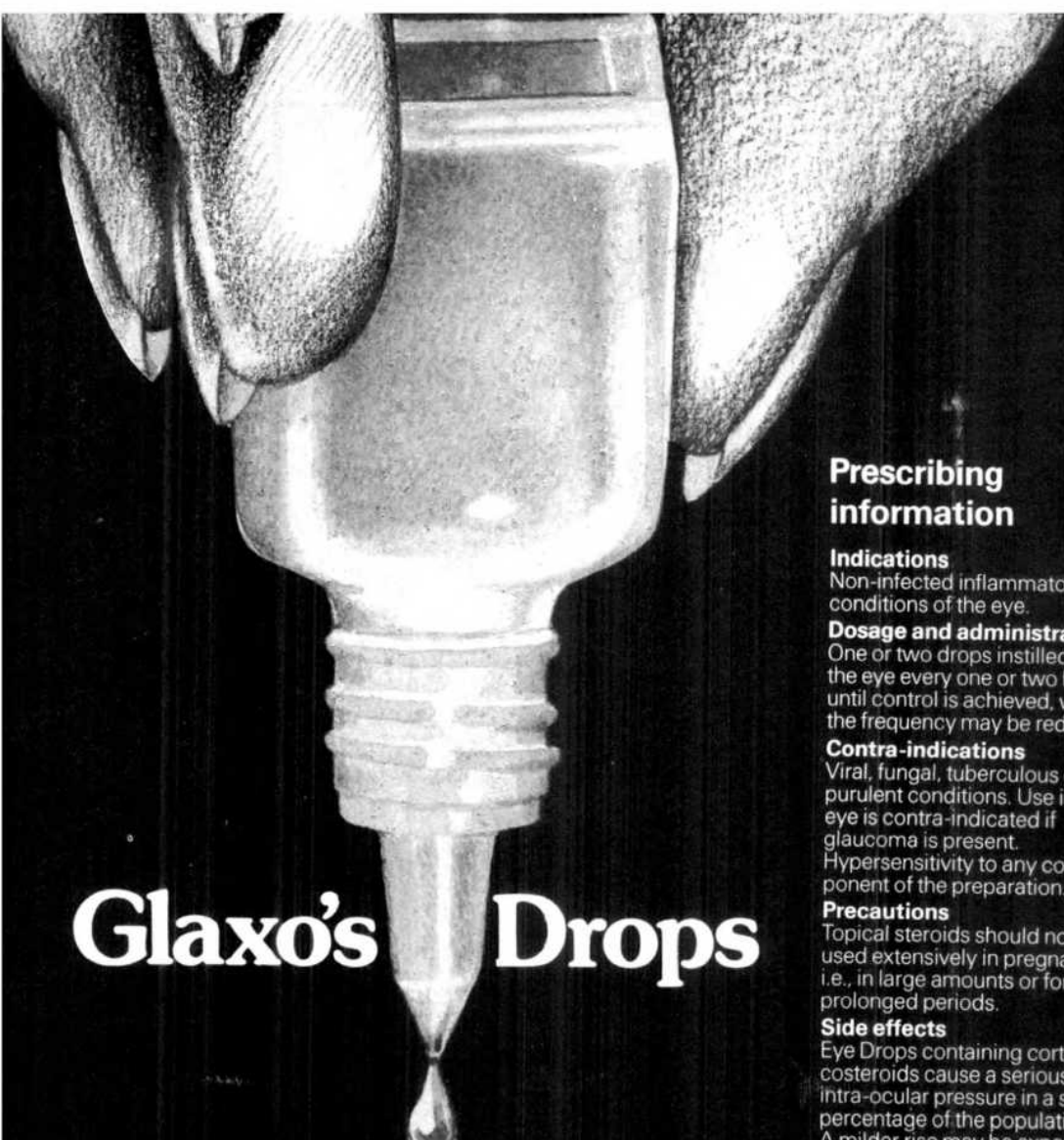
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Contrast sensitivity in children and adults

L. D. BEAZLEY, D. J. ILLINGWORTH, A. JAHN, AND D. V. GREER

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SUMMARY Contrast sensitivity functions to vertical sinusoidal gratings have been measured in 135 subjects ranging from 3 to 29 years of age. The reported contrast sensitivities for all spatial frequencies increased steadily with age, reaching adult levels during adolescence. The usefulness of these functions as a clinical test is discussed.

Contrast sensitivity to gratings has been used to investigate the physiology of the visual system in animals¹ and in man.² Recently there have been several reports of the value of such an approach to clinical practice.^{3,4} The conventional test of visual performance is the Snellen letter chart, which indicates the finest resolvable detail at high contrast. Since the visual world consists of images of different sizes at varying contrast levels, a Snellen test reveals the functioning of only one aspect of the visual system. Measurements of contrast sensitivity indicate the contrast levels required to distinguish objects of different size from their background. Contrast sensitivity function (CSF) is the graphical representation of threshold contrast to detect gratings of different spacing (spatial frequency). Several studies support the contention that CSF gives a more complete analysis of visual performance than a Snellen test. It has been found, for example, that patients with cerebral lesions who were complaining of visual problems often had severely abnormal CSFs despite normal Snellen acuities.⁵ Also CSFs have been found to be reduced in multiple sclerosis patients before any other visual disturbances were evident, suggesting the value of the technique for earlier detection of the disease.⁶

Studies of contrast sensitivity in younger ages have been restricted almost entirely to the first year of life. These have suggested markedly reduced values compared to adults.⁷ Recently a brief report on mean CSFs in different age groups has suggested that children do perform at lower levels than adults.⁸ We have investigated the possibility of extending CSF measurements to younger children and have tested a larger number of subjects to

analyse change with age. This series may form the basis for assessment of contrast sensitivity in children.

Materials and methods

Caucasian children aged 3 to 15 years and adults 18 to 29 years were subjects in this study. In each age group approximately equal numbers of males and females were tested. All subjects were volunteers. 86% of them were given an ophthalmological examination. Those over 6 years were required to have an uncorrected Snellen acuity of 6/6 or better for distance and those under 6 years an uncorrected acuity of 6/9 by the E test. The 14% not given an ophthalmological test were distributed over all age groups.

Vertical sinusoidal gratings were generated in the conventional way² on a display monitor (Tektronix 604 P31 fast-decay phosphor). The average luminance was 9 cd/m² and varied from peak to trough between 14 cd/m² and 4 cd/m² giving a maximum contrast value of 0.5, contrast being defined as $(L_{max} - L_{min}) / (L_{max} + L_{min})$ where L_{max} and L_{min} are the maximum and minimum luminances respectively of the gratings display. Observers sat 1 metre from the display, which was viewed binocularly with natural pupils through a circular window mounted on the face of the monitor such that the display subtended 6 degrees. The surround was approximately matched for luminance and colour. Room luminance was approximately 2 cd/m². An experimenter sat beside the subject and showed samples of gratings, varying the spatial frequency and contrast. The subject's task was to report when any lines were visible. Special care was taken to ensure the instructions were understood. Subjects were asked to keep their heads straight and at the measured distance; this was checked on a video-

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Table 1 *Mean contrast sensitivity at each spatial frequency for all age groups*

Age (years)	Number of subjects	Spatial frequency (cycles/degree)						
		0.25	0.5	1	2	4	8	16
3—	6	1.9	3.0	6.3	9.4	13.0	5.9	1.5
4—	17	2.0	4.7	7.4	10.5	15.0	7.2	1.9
5—	14	2.1	3.5	10.5	17.7	15.6	8.2	2.0
6—	15	1.7	5.5	11.7	23.0	32.5	13.8	2.4
7—	17	2.3	7.2	14.6	28.0	34.5	16.0	2.6
8—	14	3.1	8.2	14.4	28.2	37.0	17.7	3.1
9—12 (mean 11.5)	20	3.3	11.2	17.8	35.7	57.0	28.5	4.3
12—15 (mean 13.3)	15	4.3	14.3	19.5	58.5	75.6	32.5	7.0
18—29 (mean 22.5)	17	4.4	17.0	31.5	58.5	70.0	28.0	5.5

monitor by a second experimenter. The contrast levels were controlled by 2 attenuator knobs operated by the experimenter, a coarse control which changed contrast in 10 dB steps and a fine control with 1 dB divisions.

Threshold for detection of the grating was estimated by a modified yes/no staircase technique,⁹ the direction of the change in contrast being reversed when the report changed. The size of the contrast change was reduced at each reversal until steps of 1 dB attenuation were reached. Threshold was taken as being the contrast midway between consistent yes and no responses.

Seven spatial frequencies (0.25, 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 cycles/degree) were presented randomly so that no adjacent frequencies were tested consecutively. Between presentations of each spatial frequency, to prevent boredom or habituation effects, subjects were shown colour transparencies of a cartoon character or animals overlaying the test display and its surround; these matched the test surround in overall luminance.

Results

Data are presented on 135 subjects aged from 3 years to adult. All subjects over 4 years of age completed the test satisfactorily; in the 3–4 age group only 6 children out of 24 tested could be included. The short attention span of this age group was the main difficulty.

A clear picture emerged from this study in that there was a steady rise in mean contrast sensitivity with age. The results are presented in Table 1. There was almost no overlap between mean CSFs for each age group. For reasons of clarity a represen-

tative sample of mean CSFs in different age groups is shown in Fig. 1. Mean CSFs for all the age groups differ only in height but not in overall shape, the peak sensitivity being at about 4 cycles/degree throughout. The rate of increase in contrast sensitivity appears to be constant for all the spatial frequencies tested.

The data were analysed for sex differences in all age groups and at all spatial frequencies. None were found, except that in the 3–4 age group only girls completed the test. A typical result is shown in Fig. 2, which illustrates the rise in contrast sensitivity to a 2 cycle/degree grating with age for both sexes.

Discussion

We are reporting a series of CSF curves in a total of 135 children and adults. There is an increase with age in contrast sensitivity for all spatial frequencies which levels off in early adolescence. Since CSF measures are proving valuable in the assessment of adult visual performance it is clearly desirable to extend this test to children. We have found the assessment of CSFs by the staircase method is possible for the majority of children above 4 years and a few even younger. Although there is some individual variation in the results of the test, the general trend of increased reported sensitivity with age is clear. A test session lasts only 15–20 minutes but does in its present form require sophisticated equipment; a set of Arden plates¹⁰ modified for paediatric use might prove to be a practical solution.

There has been an earlier report of CSF in young people.⁸ The mean values of one 8-year-old and two 15-year-olds show a reduced sensitivity at low

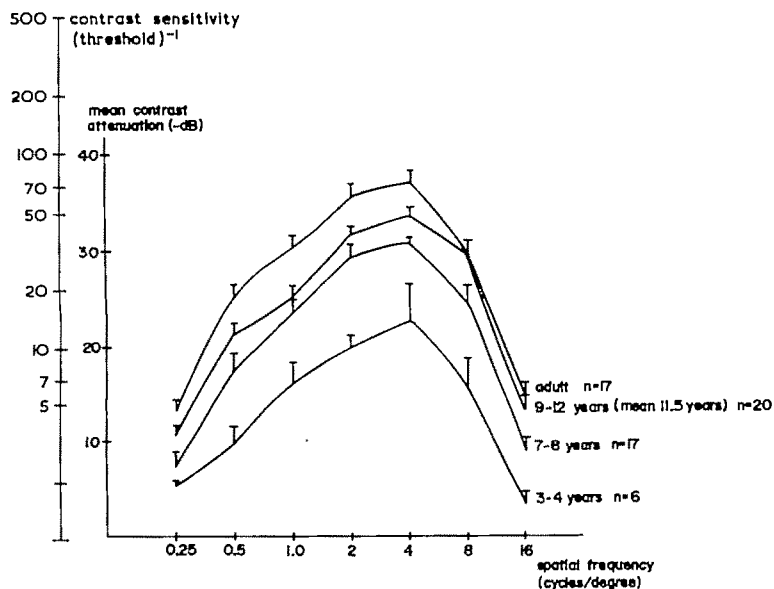


Fig. 1 Mean contrast sensitivity (reciprocal of contrast threshold) plotted as the function of spatial frequency for subjects in 4 age groups. The vertical bars represent $\pm$ the standard error of the mean. Contrast attenuation, expressed in decibels ($-dB$) is also shown.

frequencies compared to adults (18–29 years). However, in our more extensive series we have found that sensitivity for all spatial frequencies increases with age, to maximum levels in the 18–29 age group. It is possible that the older subjects (30–39 years) in this study were already showing reduced sensitivity to high spatial frequencies, a trend which was marked in the 45–66 year age group.

It is a maxim of clinical practice that early detec-

tion of visual problems is most important if therapy is to be successful. There seems to be a sensitive period in early childhood when neural connections are relatively plastic. Inappropriate neural circuitry may develop as a result of early abnormal visual experience, and this usually becomes irreversible later in life.¹¹ Studies of visual deprivation in cats and monkeys have suggested the anatomical and physiological changes which probably underlie^{12,13}

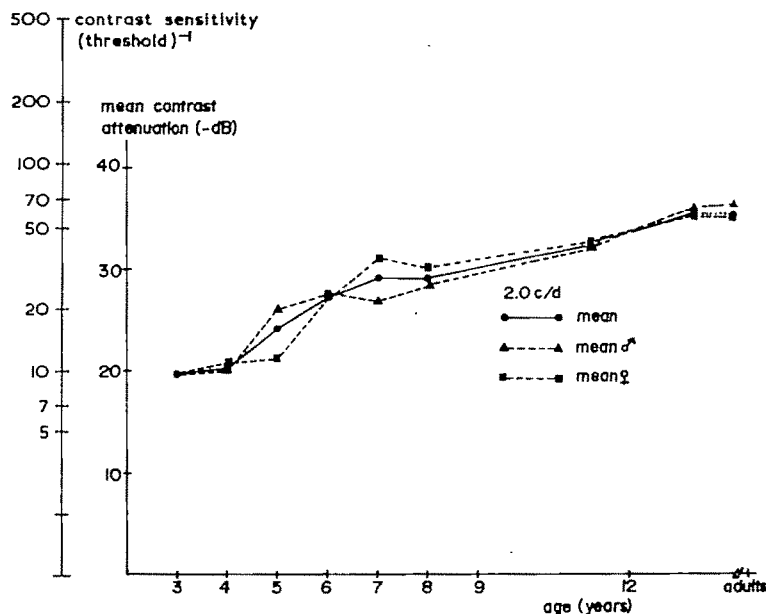


Fig. 2 Mean contrast sensitivity plotted as a function of age for a 2 cycles/degree grating; changes with age for males and females are shown. Contrast attenuation, expressed in decibels ($-dB$) is also included.

the clinical findings. In the context of early detection of visual problems, such as amblyopia, the application of the CSF may prove useful. Hess and Howell¹⁴ have found that amblyopes fall into 2 classes, those with decreased sensitivity at all spatial frequencies and others with a loss only in the higher frequencies. The prognostic value of this observation has yet to be investigated.

When this normal series is considered it appears that there are several factors which are likely to have contributed to our results. It is known that contrast sensitivity increases¹⁵ and refractive properties change¹⁶ with age. While this is reflected in our data, variations in the criteria adopted by individual subjects may also have influenced our findings. In adult subjects such differences are known to affect the height but not the shape of the CSF curve.¹⁷ The naivete of the adult subjects used in this study probably explains the rather low values we have found compared to other reports.¹⁷ Young subjects could also adopt criterion levels which vary between individuals of any one age group, accounting for some of the variability in our data. In addition there may be differences between age groups in the stringency of the criteria adopted. Use of a forced choice procedure would, according to signal detection theory,¹⁸ minimise criterion effects. However, it is a method requiring co-operation of the subject for several hours and is thus unlikely to be practical for visual assessment in children. This method provides a satisfactory estimate within a reasonable time and is thus useful for clinical practice. The significance of any deviation in a subject from our data is still a matter of judgment. As more information becomes available, it may be possible to quantify these differences.

In conclusion, we consider that use of the contrast sensitivity function may well prove valuable in conjunction with the more conventional tests of vision in children.¹⁹ It may also be useful in furthering our understanding of the development, diagnosis, and treatment of ophthalmological problems such as amblyopia.

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Tumours of the anterior uvea. III. Oxytalan fibres in the differential diagnosis of leiomyoma and malignant melanoma of the iris

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SUMMARY The diagnostic potential of oxytalan fibre demonstration in differentiating between leiomyomas and spindle-cell malignant melanomas of the iris was investigated. It was found that oxytalan fibres were abundant in leiomyomata, both between and around the tumour cells, whereas they were found in small numbers only and usually near the iris muscle in malignant melanomata. Their presence and distribution, therefore, appear to offer a satisfactory method of differentiating between these tumours. Since the human choroid and ciliary body normally contain oxytalan fibres, the above findings are not relevant to malignant melanoma of these structures. Naevi and regressing aggregates of iris melanoma cells away from the main tumour mass may similarly be surrounded by misleading amounts of these fibres.

Smooth muscle tumours of the iris have their origin in the dilator and sphincter muscles. Occasionally, however, they are found at other sites such as the anterior surface of the iris, where smooth muscle is not naturally present.¹ Leiomyomas of the iris are less common than malignant melanomata, their incidence varying between 4% and 33% of primary iris tumours.²⁻⁶

According to Verhoeff,¹ Ashton,⁴ and Reese⁵ a leiomyoma is characterised by the presence of interlacing bundles of closely packed elongated spindle cells with long, oval, palisading nuclei. The granular eosinophilic cytoplasm of the tumour cell contains longitudinal striations composed of fine, discrete, nonbranching fibrils along the body of the cell, which tend to coalesce to form larger and coarser fibrils at the cell terminal. When these features are present, there is usually no difficulty in diagnosis, but, since smooth muscle tumours share a common neuroectodermal origin with melanocytic tumours, their histological features not uncommonly overlap, often making distinction difficult and sometimes impossible. This difficulty in the differentiation of leiomyomata from melanocytic tumours has been emphasised by several workers,⁴⁻⁶ and it has been stressed that the demonstration of myogial fibrils in tumour cells by means of special stains such as

the Mallory phosphotungstic acid haematoxylin stain, the Masson trichrome stain, and the gold impregnation technique is the most important diagnostic criterion. Since myogial fibrils, which are composed of contractile proteins, have been demonstrated in tissues other than smooth muscle,⁷⁻¹⁰ it is clear that their presence cannot be regarded as a pathognomonic feature of leiomyoma. Moreover, smooth muscle fibrils may be found in malignant melanoma,¹¹ while there are cases in which the histology is in every other way typical of leiomyoma but wherein myogial fibrils cannot be demonstrated.^{4,5} In addition, because of their common neuroectodermal origin, it might be anticipated that poorly differentiated leiomyomata and melanomata of the iris would approximate to each other, and it is conceivable that there may be transitional cells between melanocytes and smooth muscle cells. While this may indicate that there is in fact no complete distinction between melanoma and leiomyoma regarding their histogenesis, there are, nonetheless, differences in their presentation as well as their clinical behaviour. Whereas death due to metastases from iris melanoma is well documented,¹²⁻¹⁶ a fatal outcome in leiomyoma is unknown.^{4,5,17}

In a separate study of the distribution of various connective tissues in the eye we were impressed by the presence of a special type of fibre in certain tumours of the iris. These so-called oxytalan fibres,

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which were first identified by Fulmer and Lillie¹⁸ in the periodontal membrane, share histochemical staining properties with elastic tissue. They are called oxytalan fibres because of their greater resistance to hydrolysis by formic acid when compared with collagen. Various stains for elastic fibres such as aldehyde fuchsin, orcein, and resorcin fuchsin do not stain these fibres, unless the tissue sections are first exposed to strong oxidising agents such as peroxymonosulphate and peracetic acid. Oxytalan fibres were later demonstrated in other sites, particularly in tissues which were subject to mechanical stress, namely tendons, ligaments and the adventitia of blood vessels.¹⁹ At present these fibres are considered to be part, along with elaunin, of the normal elastic fibre system.^{20,21} Ultrastructurally oxytalan fibres consist of a collection of microfibrils of tubular appearance with an external diameter of 12–15 nm, but unlike elastic fibres they do not have a central amorphous core.²⁰

Study of oxytalan fibres in eye has been limited, but Alexander and Garner²² have shown that they are common in a variety of pathological corneal states. We decided, therefore, to study oxytalan fibres in normal human iris and in leiomyomas and melanomas in order to see if a different distribution would help in arriving at a definitive diagnosis.

Materials and methods

This retrospective study was based on 36 iris biopsies from patients who were suspected of having a malignant tumour. Eighteen of these showed the typical features of a malignant melanoma and 10 cases showed unequivocal histological evidence of a leiomyoma. The remaining 8 cases were tentatively considered to be leiomyomas because of the presence of occasional myoglia fibres and the absence of any obvious pigmentation.

The histochemical techniques for the demonstration of oxytalan fibres were controlled by using tissues from the lower jaw of a rat. The incidence and distribution of oxytalan fibres in normal human iris, ciliary body, and choroid were studied by using fresh necropsy material. All material was fixed in 10% formol-saline, the rat jaw having been demineralised in a formic acid/formaldehyde solution and the processed tissue was embedded in paraffin. Sections were stained by Verhoeff's haematoxylin method, and by orcein and aldehyde fuchsin. In all cases parallel sections were preoxidised with a 10% solution of peroxymonosulphate for 60 minutes. Additional sections from each specimen were stained with haematoxylin and eosin, Gomori's reticulin stain, the periodic acid Schiff reaction, and by phosphotungstic acid-haematoxylin. Electron

microscopy was carried out in selected cases, sections from Araldite-embedded material being stained with uranyl acetate and lead citrate and examined by JEM-100C instrument.

In a pilot study we found that orcein stained oxytalan fibres rather weakly, and, since the fibres were stained a brownish colour, they were not easily identified in pigmented tumours. Moreover, transversely cut oxytalan fibres may be confused with melanin pigment. Orcein staining was thus unsatisfactory for the demonstration of oxytalan in the iris, and only those results obtained by aldehyde-fuchsin staining will be referred to.

Results

Oxytalan fibres were not demonstrated in normal iris but were always present in the ciliary body and choroid. A section stained with aldehyde-fuchsin was considered positive for oxytalan fibres only when brilliant purple delicate fibres were demonstrated. Sections which were not previously oxidised showed the presence of aldehyde-fuchsin-positive elaunin fibres in 10 out of 36 iris tumours. These fibres stained a weakly positive colour and were present in the media of large blood vessels and among the tumour cells of leiomyomas. In all cases oxytalan fibres were more abundant in those areas which contained elaunin fibres.

Smooth muscle fibrils were identified by phosphotungstic acid-haematoxylin (PTAH) staining, a known case of a leiomyoma of the uterus acting as a control. In tumours where PTAH staining revealed the presence of large numbers of intracellular myoglia fibres (Fig. 1), oxytalan fibres were numerous in the stroma (Fig. 2). Furthermore, in some cases the cytoplasm of the dilator muscles appeared to stain with aldehyde fuchsin following oxidation, suggesting that they may contain soluble precursors of oxytalan fibre. It is possible, however, that the actomyosin molecules in myoglia fibres themselves become receptive to aldehyde fuchsin following oxidation.

In melanocytic tumours of the iris oxytalan fibres were present only in small numbers and were usually confined to the regions of the sphincter and dilator muscles and the media of large blood vessels where smooth muscle is easily demonstrable (Fig. 3). In one tumour which extended into the cornea, however, oxytalan fibres were found in the substantia propria adjacent to the tumour (Fig. 4). This possibly reflects the propensity of the cornea to accumulate these fibres in response to a variety of pathological injuries²² rather than a tumour-specific response. One tumour which had been diagnosed as a leiomyosarcoma recurred 5 years

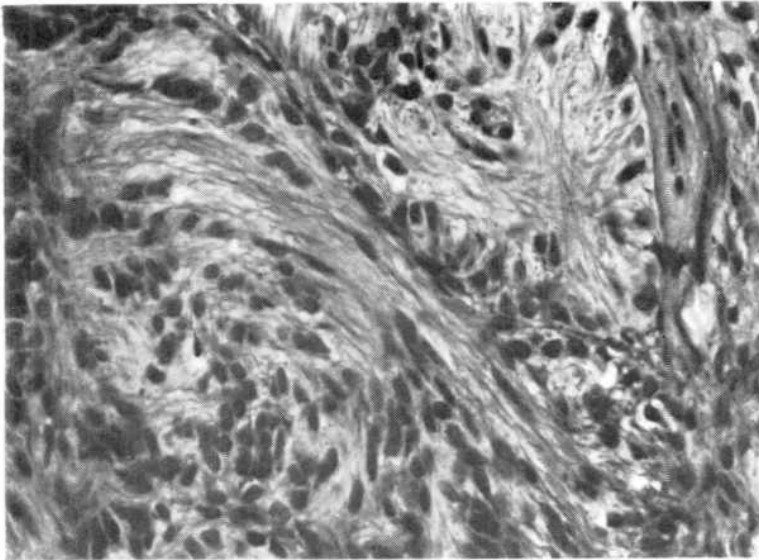


Fig. 1 Section of a leiomyoma of the iris stained with PTAH, demonstrating the intracytoplasmic myofibrils. ($\times 660$).

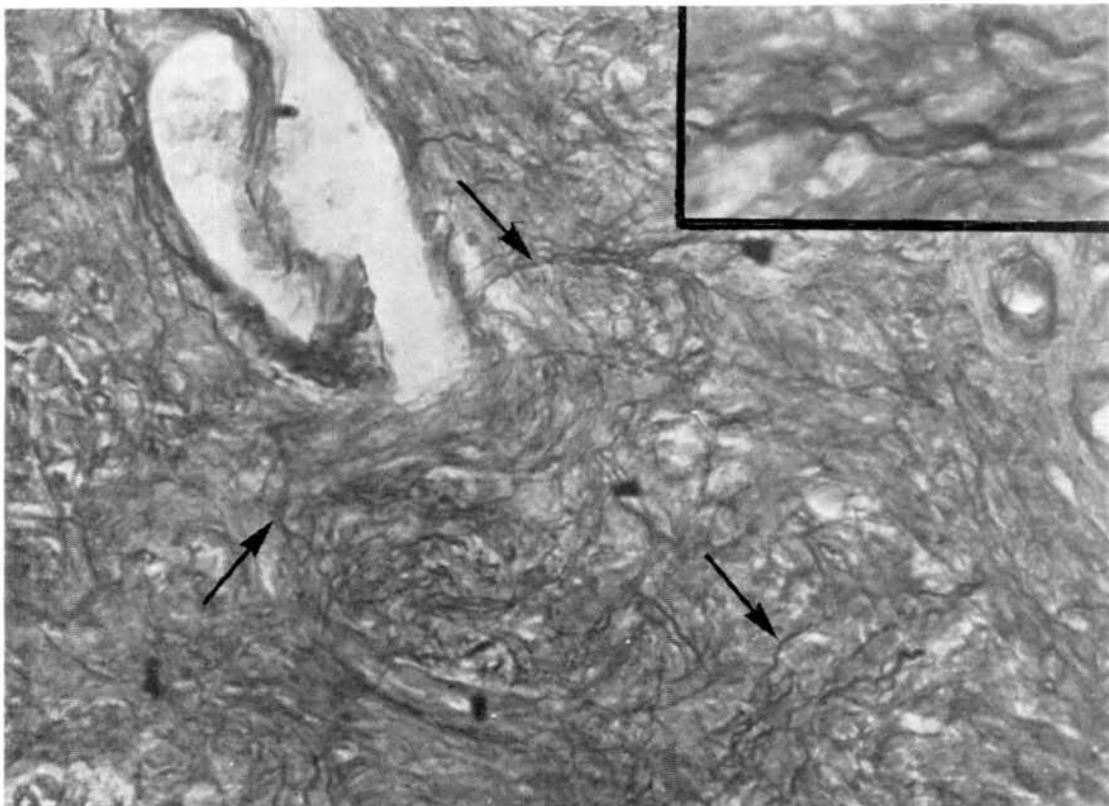
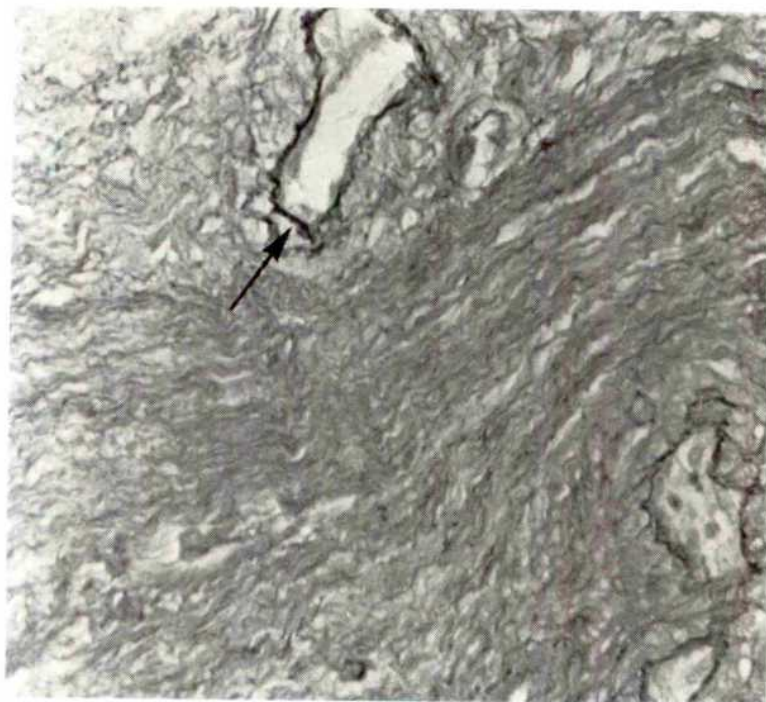


Fig. 2 Section of a leiomyoma of the iris showing darkly stained extracellular oxytalan fibres (arrows). ($\times 960$). The inset shows the same fibres under higher magnification).

Fig. 3 Section of a malignant melanoma of the iris. Note that the oxytalan fibres are present only in association with the blood vessels. ($\times 680$).



later. The enucleated eye now showed a typical diffuse, infiltrating, pigmented malignant melanoma. The patient died at a later date with liver metastases. Stained sections of the recurrent iris tumour showed occasional oxytalan fibres in the region of the dilator and sphincter muscles, but not in association with the tumour. In cases of melanocytic tumours that arise from the root of iris, there may be an abnormal accumulation of oxytalan fibres which can be traced to the ciliary body, which, unlike the iris, normally has a rich supply of oxytalan and elaunin fibres. Conversely, smooth muscle tumours of the iris were found to be rich in oxytalan fibres usually associated with thick bundles of collagen both between and around the tumour cells. The fibres were arranged either singly or in bundles of varying length. The short fibres were usually thick and curved and sometimes ended in a club-like swelling. The long fibres were usually thin and in many instances coalesced to form bundles. In the region of the dilator muscles they often ran a wavy course parallel to the pigment epithelium of the iris, and similar bundles were also found in the region of the sphincter muscle. The oxytalan fibres not infrequently showed a branching pattern in both the smooth muscle tumours of the iris and the uterus. Although the arrangement of these fibres in the smooth muscle tumours of the iris usually varied, they sometimes showed a honeycomb

pattern such as is seen in uterine leiomyomas.

The oxytalan fibres demonstrated in the present study failed to stain with Gomori's reticulin stain, Masson's trichome, PAS, and phosphotungstic acid haematoxylin. Mature elastic tissue was not found in any of the tumours.

The presence of oxytalan fibres within a leiomyoma was confirmed by electron microscopy (Figs. 5 and 6).

Discussion

A smooth muscle tumour is mesodermal in origin except in the iris, where the lesion arises from the dilator and sphincter muscles, which originate from multipotential neuroectodermal cells of the outer layer of the optic vesicle. This layer also gives rise to the pigment epithelium of the retina and the ciliary body, and in the iris there is a transition to smooth muscle. Since it is well established that melanocytes arise from the neural crest,²³ it would appear that melanocytic as well as smooth muscle tumours of the iris have a common ancestry in the neuroectoderm (Fig. 7). It is not surprising, therefore, that these tumours share similar potentials for morphological differentiation and dedifferentiation.^{4,6} As stated previously their histological features may overlap, making their differentiation difficult. This difficulty in differentiation between

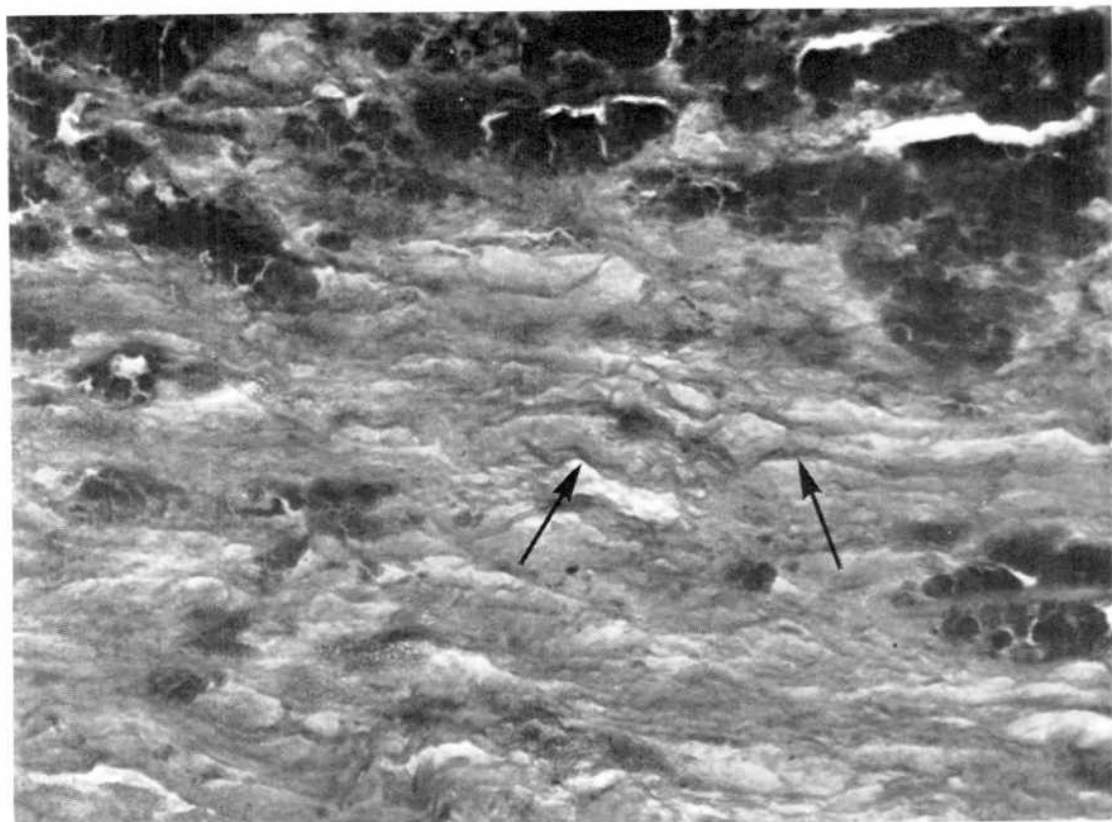


Fig. 4 Section of the cornea infiltrated by malignant melanoma originating within the iris. There are some oxytalan fibres in the corneal stroma which were not seen, however, in the main tumour. ($\times 960$).

leiomyoma and melanoma of the iris is accentuated by the regular spindle cells devoid of mitotic figures characteristic of the latter tumour. Furthermore, although leiomyomata elsewhere in the body are generally nonpigmented, some smooth muscle tumours of the iris may contain melanin, especially those arising from the dilator muscle, which, in contrast to the sphincter pupillae, shows only partial differentiation.^{5,24} On the other hand many melanocytic tumours lack pigment or are only lightly pigmented, so that differentiation based on the pigment content alone is impossible. Similarly intranuclear cytoplasmic inclusions, which are a feature of spindle cell melanoma of the uvea,²⁵ may also be present in leiomyoma of the iris.

Although in the past the demonstration of myoglia fibrils in spindle cell tumours of the iris has been regarded as the most important criterion in the diagnosis of a leiomyoma, recent immunological and electron microscopical studies have shown that non-muscle tissues of the eye as well as spindle cell melanomata also contain similar fila-

ments.¹¹ It is clear, therefore, that the presence of myofilaments alone cannot be regarded as a pathognomonic feature of leiomyoma. However, when myoglia fibrils are present together with other histological characteristics of a smooth muscle tumour, i.e., interlacing elongated spindle cells, palisading cigar-shaped nuclei, absent pigmentation, and rich vascularity, there is usually no difficulty in diagnosis. But there are cases in which the histology is in every way typical of a leiomyoma but where myoglia fibrils cannot be demonstrated.⁴ Moreover in some cases of malignant melanoma of the iris there may be secondary hyperplasia and hypertrophy of the sphincter and dilator muscles due to neoplastic infiltration, and it has been suggested that uveal melanomas produce a growth-stimulating substance that can stimulate the growth of normal uveal cells.²⁶ These hyperplastic smooth muscle cells usually show myoglia fibrils when stained with PTAH, which may lead to a mistaken diagnosis of leiomyoma.

Although melanoma and leiomyoma share the

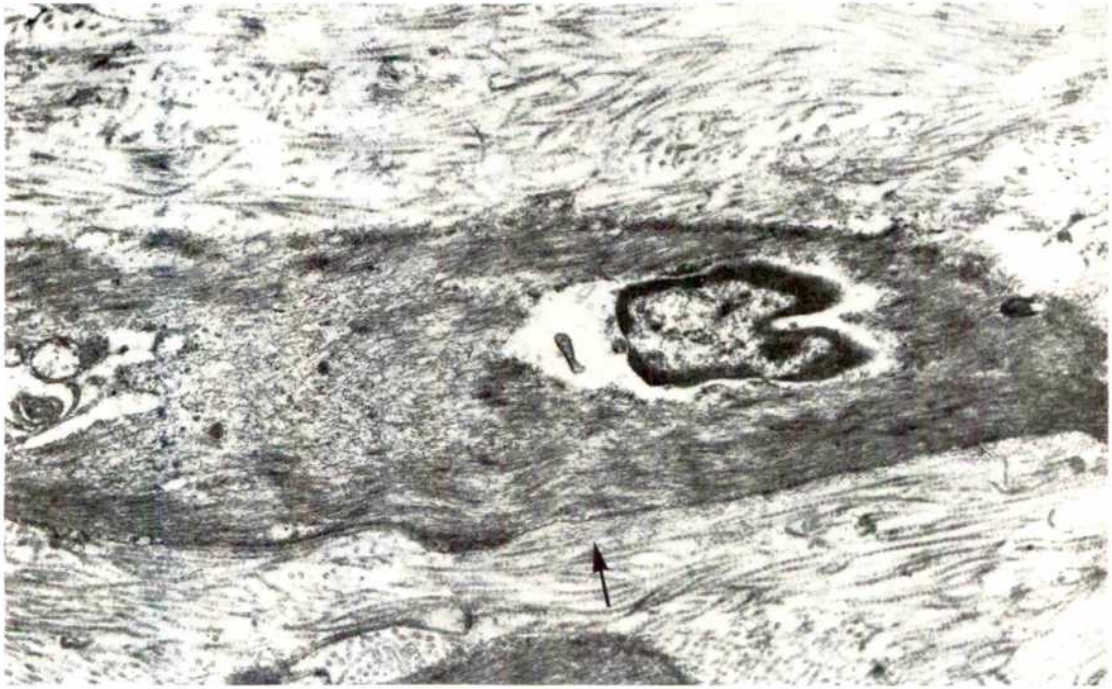


Fig. 5 Electron micrograph of a leiomyoma showing intracellular actomyosin filaments. Immediately outside the muscle cell there is a collection of oxytalan microfibrils (arrow) which appear very much smaller than the prominent collagen fibres. ($\times 14\,500$).

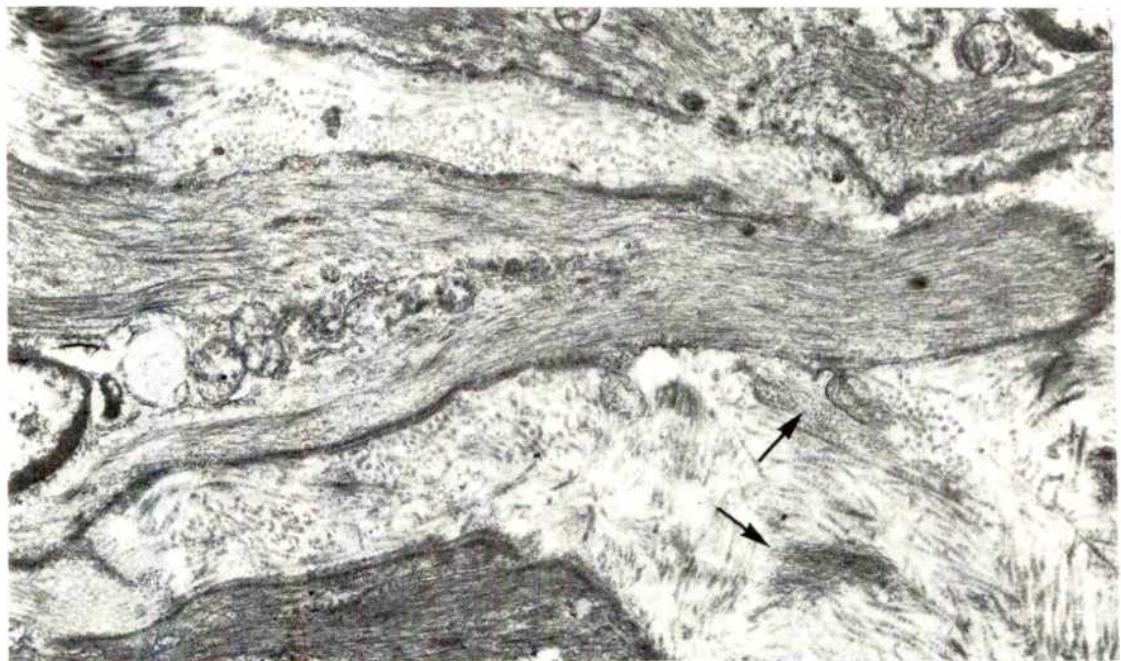


Fig. 6 Oxytalan microfibrils in another leiomyoma. The electron micrograph shows very clearly the localised collections of these fibrils (arrows). ($\times 14\,500$).

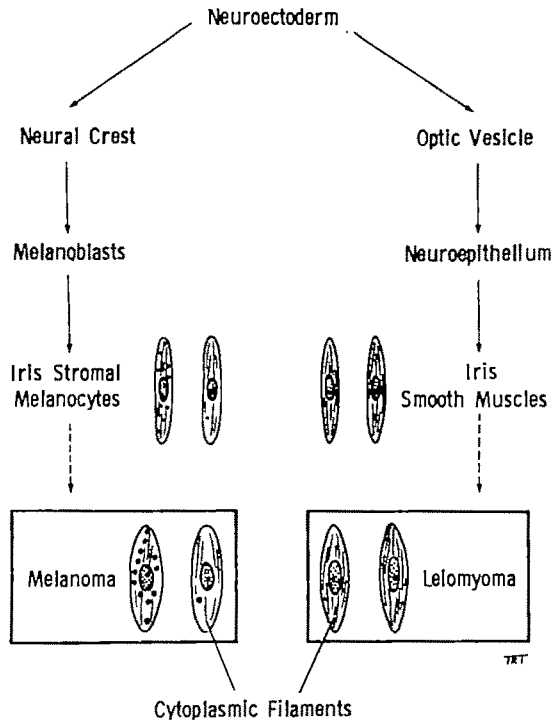


Fig. 7 To show the common ancestry and the morphological relationship between melanoma and leiomyoma of the iris.

same histogenesis because of their embryological origin, there are differences in their clinical behaviour. While leiomyomatous tumours may be locally invasive, they do not metastasise.^{4, 5, 17} In addition, we have not recorded any instance of metastasis in a study of over 200 primary tumours of the iris in which the patients were followed up for periods between 7 and 30 years. Since malignant melanomas of the iris do metastasise occasionally¹²⁻¹⁶ it is important to differentiate these 2 tumours for prognostic reasons. In the present study we have included only those leiomyomas which satisfied all the criteria of smooth muscle tumours.

Leiomyomatous tumours were rich in oxytalan fibres, while melanocytic tumours were usually devoid of such fibres except in the walls of large blood vessels which normally contain smooth muscle cells. Some melanocytic tumours appeared to contain a few oxytalan fibres, which on close examination were found to be associated with the sphincter and dilator muscles. In no instance, however, did any of the melanocytic tumours contain histochemically recognisable oxytalan fibres between the tumour cells. Ultrastructural examination of tissue from 3 such cases failed to demonstrate the characteristic 12 nm diameter oxytalan fibrils.

A feature of great interest is the intimate relationship between oxytalan fibres and smooth muscle cells. We found that this close proximity was a constant feature, not only in the leiomyomas of

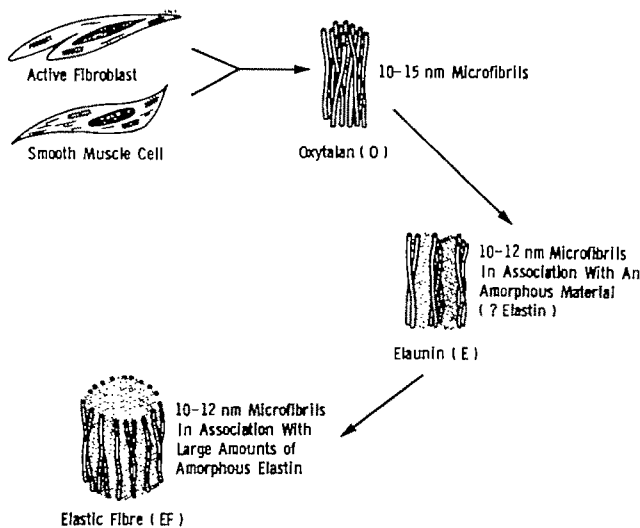


Fig. 8 Diagram speculating on the origin and maturation of elastic fibres (i.e., $O \rightarrow E \rightarrow EF$). The maturation process may be arrested at O or E in both normal and abnormal tissues.

SPECULATIVE DIAGRAM TO SHOW THE ORIGIN AND MATURATION OF ELASTIC FIBRE (i.e. $O \rightarrow E \rightarrow EF$).
THE MATURATION PROCESS MAY BE ARRESTED AT O OR E IN NORMAL AS WELL AS PATHOLOGICAL TISSUES

the iris but also in leiomyomas of the uterus and in the hypertrophic blood vessels of the tumours. It is relevant in this context that in an experimental study performed on growing rats^{27, 28} the authors reported autoradiographical evidence of the incorporation of labelled proline in proteins synthesised by smooth muscle cells. They also demonstrated that these cells were responsible for the elaboration of the three major constituents of connective tissue, i.e., collagen and the 2 components of elastic fibre, the microfibrils and elastin. The role of smooth muscle in the production of connective tissue in man has also now been confirmed.²⁹ Since oxytalan fibres are currently considered to be a member of the normal elastic fibre system,^{20, 21} it is conceivable that these fibres are also produced by smooth muscle cells. Furthermore, the intimate relation of these fibres with smooth muscle, the presence of elaunin, and the occasional staining of smooth muscle cells by aldehyde fuchsin following oxidation are points in favour of oxytalan fibres being the product of smooth muscle cells (Fig. 8).

Since mature elastic fibres were not present in any of our cases, it is possible that oxytalan fibres are either a separate class of elastic tissue or simply represent an arrested maturation. The appearance of oxytalan fibres was not related to time because we observed them in tumours as early as 3 weeks and as late as 14 years.

In the case of malignant melanoma of the iris which infiltrated the cornea, the origin of oxytalan fibres in the corneal lamellae is obscure, but it is possible that there are cells other than fibroblast and smooth muscle (e.g., keratocytes) that can synthesise these fibres (Fig. 8).

Experience gained from the malignant melanoma which was originally diagnosed as a leiomyosarcoma illustrates that the incidence and distribution of oxytalan fibres are reliable diagnostic criteria. The present study also suggests that oxytalan fibres in the tumours of the iris are the product of smooth muscle cells.

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Book reviews

The Elderly Person with Failing Vision. A report to the Department of Health and Social Security, May 1979. Pp. 34. £2.00. The Disabled Living Foundation: London, 1979.

This booklet summarises the outcome of a series of seminars held under the aegis of the Disabled Living Foundation on the subject of 'The Elderly Person with Failing Vision', which had been held in various areas of the country between 1976 and 1978. A considerable amount of interesting information in respect of the problems of the aged is contained in the report, and a number of general recommendations are made, the implementation of which on a widespread basis would be likely to result in a considerable alleviation of the visual problems of the elderly. The factors which stand out as being of particular importance include the better understanding and education of the primary health care personnel concerned with the elderly; the very important part which adequate and appropriate lighting plays in achieving the best performance on the part of individuals; and, perhaps above all, the immense importance of the interrelationship between only slightly defective vision and the many other handicaps which may afflict the elderly.

A recurrent theme of the report suggests that, rather than there being necessarily a need for more resources and more knowledge, a better and a more selective application and distribution of existing facilities and information might yield the greatest benefit.

The report serves to emphasise that the visual difficulties of a large and increasing section of the population need to be a prime concern, not to be subordinate to the many other concerns of the aged, of all those working in the ophthalmic and visual fields. M. J. GILKES

Ophthalmic Dispensing. 3rd edn. By RUSSELL L. STIMSON. Pp. 697. \$29.75. Charles C Thomas: Springfield, Illinois, 1979.

This is the third edition of Russell Stimson's well-known book on ophthalmic dispensing. Written primarily for American student opticians, it covers every aspect of optical dispensing from the issue of a prescription for spectacles to the final fitting and adjusting of the appliance.

The first 4 chapters provide basic information on ocular anatomy, physiology, and optics. The historical development of various ophthalmic lens types is then traced, and chapters 6, 7, and 9 outline the principles of spectacle frame fitting. The cosmetic aspect of dispensing is covered and advice is given generally throughout the book on how to deal with patients courteously and efficiently. Chapters 10 and 11 on prescription analysis are very helpful, and the remainder of the book consists of individual chapters devoted to specific areas of interest such as the spectacle correction of aphakia, vocational lenses, protective lenses, low vision aids, and orthoptic devices. Additional references are given at the conclusion

of each chapter, and at the end of the book a glossary of terms is provided followed by a good page index.

This third edition is a sizeable volume, and the factual information it contains could probably be condensed into a less formidable book. Nevertheless, the author has presented here a textbook that is interesting and easy to read. The wealth of information this book contains cannot fail to provide anyone who reads it with a fuller understanding of the difficulties that patients can experience with spectacles. It is recommended reading for all dispensing opticians. ANDREW MILLIKEN

Perimetric Standards and Perimetric Glossary of the International Council of Ophthalmology. Ed. J. M. ENOCH *et al.* Pp. 133. Dutch Guilders 55.00. W. Junk: The Hague, Netherlands, 1979.

With the appearance of more and more devices of varying sophistication for measuring the visual field there arises the increasing need to compare their performances, and this requires strict standards for comparison. This booklet is helpful in this respect, being concerned with the definition of terms used in perimetry and with the standardisation of apparatus and procedures. A few years ago an International Perimetric Society (IPS) was formed, and so it is not surprising that the value of a multilingual perimetric glossary was soon recognised and work began on its compilation.

The first 14 pages deal with perimetric standards. This was the work of a committee chaired by Jay Enoch, with members from Germany, France, Switzerland, UK, the Netherlands, and Belgium, who were selected at a meeting of the Research Group on Standards of the IPS. The definitions given are straightforward and precise, and similar care is evident in the treatment of other topics such as target specification, contrast, duration of presentation, and image sharpness. Matters of practical interest such as the rate of target movement in kinetic perimetry and the influence of attention signals receive brief mention.

The remaining 118 pages of the book are occupied by the perimetric glossary, in which 515 terms covering the physiological, pathological, and technical aspects of the subject are given in 10 languages—English, French, German, Spanish, Russian (in Roman characters), Italian, Swedish, Dutch, Polish, and Japanese. The terms are given in 5 groupings: stimulation, perception, technique, normal visual field, and pathology. The translation was undertaken by an international committee of 16 members, the editor being Guy Verriest, and the resulting multilingual glossary has been submitted to the Concilium Ophthalmologicum Universale. There is also an alphabetical index of the English terms.

It is obvious that a lot of thought has gone into the wording of definitions, into compiling a comprehensive list of terms, and into their translation. The main purpose has been to contribute to international understanding in the usage of perimetric terminology and to help to develop research in all aspects of the visual field. This has clearly been achieved, and the booklet is likely to remain as a standard of reference for some time.

J. GLOSTER

Proceedings of the Paul Cibis Club, 1979. (Eds.) EDWARD OKUN and GLEN PAUL JOHNSTON. Pp. 215. \$20.00. The Paul Cibis Club: St. Louis, Missouri, 1979.

To eavesdrop a conversation between enthusiasts, when those enthusiasts are expert in their field, is a stimulating experience. This report of the Paul Cibis Club is just such an opportunity, where the reader may glean pearls of information about a variety of topics in the surgical management of a number of difficult retinal problems.

The slant of this meeting is towards vitrectomy. The guest lecturer, Dr Stephen Ryan, who has to do much more than deliver an address ex cathedra, joins the cut and thrust of debate in many of the presentations after giving a valuable dissertation on massive periretinal proliferation, its pathology, and treatment by vitrectomy, with particular reference to posterior segment trauma.

The remainder of the contributions cover many different subjects; most are in the form of case reports with commentary, but some are concerned with points of technique. The topics discussed include the drainage of subretinal fluid under direct vision, the value of estimating carcinoembryonic antigen, the use of liquid silicone, its technique and indications, the management of postoperative haemorrhagic and serous choroidal detachment, glaucoma as a mode of presentation in retinal detachment, macular holes, and postoperative gas injection in failed detachment operations. The problems of diabetic retinopathy with traction retinal detachment are also discussed, along with other specific topics which include the extraction of a fish hook from the posterior segment, the management of posterior dislocation of the lens in cataract surgery, and sympathetic uveitis following vitrectomy.

Workshop presentations are not carefully weighed didactic statements. This would be to lose the stimulus of the occasion. So despite the care of the contributors to be fair to viewpoints at variance with their own the critic may at times find, as he would expect, that the presentations are bounded by the views of this particular school. But it is a good school.

The book is a good one which will encourage, stimulate, and refresh the mind of the retinal surgeon, who will also find useful practical tips in dealing with difficult circumstances. The general ophthalmologist will gain insight into the current 'state of the art', which will help immensely in deciding when to pass a case to the expert.

D. W. HILL

Les Syndromes Opto-Chiasmatiques. By P. Bregéat. Pp. 196. No price given. Masson: Paris, 1979.

This book by one of the doyens of European neuro-ophthalmology provides a review of the author's extensive experience, with support from his collaborators in neuroradiology and neurosurgery. Written in French, it is well illustrated with diagrams, visual fields, x-rays, and a number of CT scans. Contents include a brief review of the anatomy, followed by sections on the clinical and radiological features of the varied lesions producing parasellar lesions. It is sad, however, to see the Edinger-Westphal nucleus still represented as two

widely separated nuclei, so long after Warwick's work, and the diagrams and clinical implications of the junctional scotoma are not fully emphasised. Most classical subjects are discussed, but the endocrinological side could be elaborated, and the omission of septo-optic dysplasia merits rectification in a future edition. The bibliography is limited largely to the French literature, references are not related to the text, and most readers will not benefit from a number of references to an unpublished symposium. This well produced, small, and handy book provides a good general view of the chiasmal region.

M. D. SANDERS

Ophthalmology: Principles and Concepts. 4th edn. By F. W. NEWELL. Pp. 638. £18.75. C. V. Mosby: London, 1979.

Earlier editions of this book have all been reviewed in the *BJO* in glowing terms. Despite advances in technology over the last 10 years this text keeps up to date and well in touch with new methods and their findings. Since the last edition sections have been added on phagocytosis and renewal photoreceptor outer segment discs, the aldose-reductase pathway of galactose cataract formation, improved cytological methods, photocoagulation, microsurgery, intraocular lenses, vitrectomy, enzyme assay of fibroblast cell culture, tear film abnormalities, computed tomography, ultrasonography, corneal endothelial function, visual evoked potential, glaucoma management, mechanisms of amblyopia, soft contact lenses, and new antibiotics. As the author so rightly states, 'These and other changes have made ophthalmology far different from what it was a generation ago'.

The layout is in 4 parts: basic mechanisms, history taking and examination of the eye, diseases and injuries of the eye, and systemic diseases and the eye. To meet the needs of nonophthalmologists diseases are discussed without emphasis on refraction, optics, biomicroscopy, and related areas. Discussion of systemic disorders emphasises the basic abnormality of the primary disease process rather than involvement of a particular portion of the eye. The book covers 627 pages, with an excellent glossary and index. Many of the illustrations are photographs of a high standard, and the text itself is readable and compressed without being disjointed. At the end of each chapter there is a bibliography which picks out the important contributions to the subject discussed. The fourth section on systemic diseases and the eye is particularly well designed, highlighting the close association of ophthalmology with systemic disease and written in such a way as to inform not only ophthalmologists but also general physicians.

S. J. H. MILLER

Behçet's Syndrome. Eds. T. LEHNER and C. G. BARNES. Pp. 323. £16.40. Academic Press: London, 1979.

This book results from a symposium held at the Royal Society of Medicine, London, in February 1979 and organised by Professor T. Lehner (professor of oral immunology, Guy's Hospital) and Dr C. G. Barnes (department of rheumatology, London Hospital).

Ophthalmologists will be interested that a first description of Behçet's syndrome is attributed to Hippocrates (fifth century BC) who is reported to have described aphthous ulceration, genital ulceration, and iridocyclitis. Lacking our present facilities, he wrote about 'watery ophthalmies of a chronic character with pains, fungous excretions of the eyelids externally and internally which destroyed the sight of many persons'.

The ophthalmic contributions included a report of 30 patients from Moorfields, in which visual acuity of 6/60 or less developed in 43% of the patients about 3 years after the first visual symptoms. Fifteen patients reported from St Thomas's Hospital were classified into 4 groups on the fundus and fluorescein angiographic appearances: (1) perivenous and capillary leakage; (2) venous occlusion; (3) retinal infiltration; (4) atrophic stage. It is interesting that venous occlusion was seen in 4 cases and was associated with a steroid responsive hyperviscosity syndrome. HLA B5 was seen in 71% of cases. A further series of 32 patients from Guy's Hospital show the ocular features and emphasise the association with HLA B5. Continued ocular observation of patients with Behçet's syndrome is recommended, as one asymptomatic patient had mild uveitis.

Behçet's syndrome is a good example of a systemic circulating immune complex disorder, as was reflected in papers on oral and genital ulceration, gastrointestinal changes, joint changes, neurological involvement, and renal involvement. Immunological studies comprise one-third of the book, and, though abnormalities are seen in most of the patients, few diagnostic tests emerge. Therapy remains based on steroids and azathioprine, and transfer factor and levamisole tend to have complications greater than their potential therapeutic benefits.

This is an interesting well produced book, which emphasises 'the multisystem involvement of Behçet's syndrome. The ophthalmologist plays a vital role in the detection and management of this condition, which tends to cause blindness in young people. M. D. SANDERS

Obituary

Charles R. Kanagasundaram, MBBS, DO

Charles Kanagasundaram died on 5 July 1980. He was born 57 years ago into a gifted Christian Tamil family in Ceylon, where he went to school, and qualified as a doctor. After 5 years in general medical duties in the Government Health Service he came to Great Britain in 1952, where he held junior ophthalmic posts at Coventry and Warwickshire Hospital and the Royal Eye Hospital, London, then becoming senior registrar at the Wolverhampton Eye Hospital and the United Birmingham Hospitals. In 1962 he became consultant at Newcastle upon Tyne General Hospital and Walkergate Hospital and took care of clinics at Hexham and Berwick. His publications up to that time indicated what were to be the outstanding features of his work as a consultant, namely, anterior segment surgery and clinical photography.

It was always a delight to watch Charles operating: he made it look so easy and graceful and one learned much by doing so. At this time, he brought to ophthalmology the fruits of his other hobby—engineering—and he applied his logical mind and knowledge of engineering principles to surgical techniques and to the improvement of surgical instruments and sutures. Indeed he actually manufactured some instruments of great delicacy in his own workshop, and he repaired instruments that the professional instrument makers claimed were beyond them.

His shrewd but sympathetic understanding of people combined with his foresight and willingness to spend much time and effort mastering all the relevant facts, enabled him to make a valuable contribution to the plans for the future of ophthalmology in Newcastle. His own absolute integrity and lack of personal ambition made his judgments particularly valuable.

A naturalised British citizen who enjoyed living in Britain, he nevertheless retained a great love for his own country and people. On his visits to Sri Lanka he was invited by the Association for the Advancement of Scientific Students of Sri Lanka to lecture in Colombo and spent part of his holidays operating in hospital there. He was vice-chairman of the Standing Committee for the Economic Betterment of Underprivileged Tamils (SCOT) and this entailed regular journeys to London.

After a massive stroke his recovery was encouraged by his devoted wife, and his inventive mind was put to solving the problems he encountered, so that he had already designed devices for use by paraplegics and was taking steps to see that they were manufactured, when he had a further coronary occlusion, which proved to be his last illness.

His sense of humour gave him great delight in the fact that his young son is particularly good at English and that his daughter shows signs that she has inherited his own engineering aptitudes.

M.A.C.J.

Brian Zwick, MB, BS, DOMS

Brian Zwick, who died recently after a long and trying illness, was an associate member of the Faculty of Ophthalmologists and a valued member of the staff of the Ophthalmic Department of the London Hospital.

He was born in Ilford in 1917, and was educated at Aldenham School and the London Hospital, where he qualified in 1941. After a year of house appointments he joined the RAMC, and was sent to Egypt. He worked in the 13th and later the Scottish General Hospitals, and became a graded ophthalmologist at No. 1 General Hospital. On demobilisation in 1947 he was at the No. 12 GH in Palestine.

Returning to the London Hospital, he made his career there. Having taken the DOMS in 1948 he became chief assistant, and after this continued to work there as an SHMO. He took over Preston's practice in Ilford, where he became universally known and deeply respected. He was an invaluable member of the eye department, with an enormous capacity for hard work, and was never daunted by the seemingly endless stream of patients, being the first to arrive and the last to leave

except when Wimbledon, Covent Garden opera, or Glyndebourne proved irresistible. In conjunction with Ambrose King and Eric Dunlop he did valuable investigations into the correlation of ocular signs with the various stages of syphilis, some results of which have been published. His seniors and equals recognised his exceptional judgment in diagnosis, but it was the succession of housemen who really most appreciated his gifts as an outstanding teacher. He enjoyed inculcating a logical and reasoned approach to a problem, and many ophthalmologists can look back to their first house appointment at the London, where he taught them to think lucidly.

He is greatly missed in every part of the London Hospital and by his patients in East London. Our deepest sympathy is due to his wife, Pat, also a doctor, and to his children.

J.A.

Notes

New journal of visual impairment

The *British Journal of Visual Impairment* is a new quarterly journal being launched this year by Newton Mann Ltd and the Visual Impairment Association (Great Britain and Ireland). Each issue will be linked to a theme, and initial themes will include co-operation, co-ordination, and communication in the provision of services; diabetes and failing vision; and low vision/low vision aids. Details from Newton Mann Ltd, Sherwood House, Matlock, Derbyshire DE4 3LT.

Register of research on blindness

The 1980 edition of the *International Register of Research on Blindness and Visual Impairment* contains: a list of projects on nonmedical research and innovation practice for the blind and visually impaired; a list of the main organisations in each country, of and for the blind and visually impaired; a list of sources of information including periodicals, abstract journals, and information services. The price is £10.00, which includes packing and airmail postage for destinations outside Europe. Obtainable from Dr J. M. Gill, Warwick Research Unit for the Blind, University of Warwick, Coventry CV4 7AL.

Pakistan conference

The Ophthalmological Society of Pakistan, North Zone, Lahore, will hold its annual conference on 19-21 December 1980 at F. J. Medical College, Lahore. Courses will be conducted on detachment of retina, anterior vitrectomy, and fluorescence angiography. Further details from Dr Dil M. Mirza, Cairns Hospital, Allama Iqbal Road, Lahore 5, Pakistan.

Symposium on the anterior segment

The Eye Foundation of America will hold a symposium on the anterior segment on 20-21 February 1981, at New Orleans, Louisiana. Fee: \$200 for practising physicians, none for residents and fellows. Details from Dr Kenneth G. Haik, The Eye Foundation of America, 823 Maison Blanche Building, New Orleans, Louisiana 70112, USA.

Contact lens fitting

The Rudolph Ellender Medical Foundation will hold its 21st annual instructional course in contact lens fitting at New Orleans on 3-5 April 1981. Details from the Secretary-Treasurer, Rudolph Ellender Medical Foundation Inc., 136 So. Roman Street, New Orleans 70112, USA.

International Intraocular Implant Club

Dr Cornelius D. Binkhorst has been nominated to deliver the second Ridley medal lecture during the joint meeting of the IIIC with the American Intraocular Implant Society during the International Congress of Ophthalmology in San Francisco in November 1982.

International Strabismological Association (ISA)

A meeting of the ISA will be held near San Francisco shortly before the main International Meeting in November 1982. Members of the ISA should notify the Secretary-Treasurer, Dr A. Huber, University Eye Clinic, CH-8091 Zurich, Ramistrasse 100, Switzerland, of any change in address since the last meeting in Kyoto, so that they can be informed about the details of the meeting. Also, any intending new members of the ISA should contact Dr Huber for details about this.

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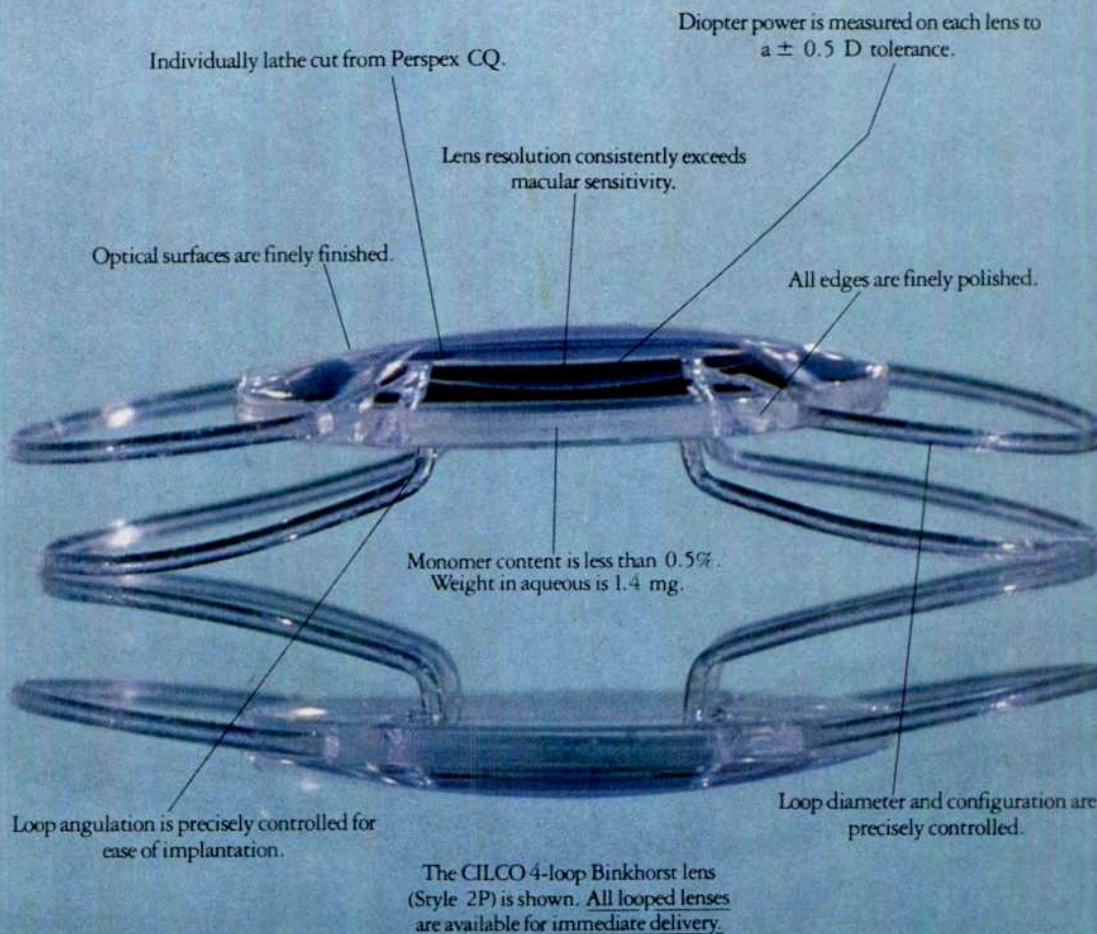
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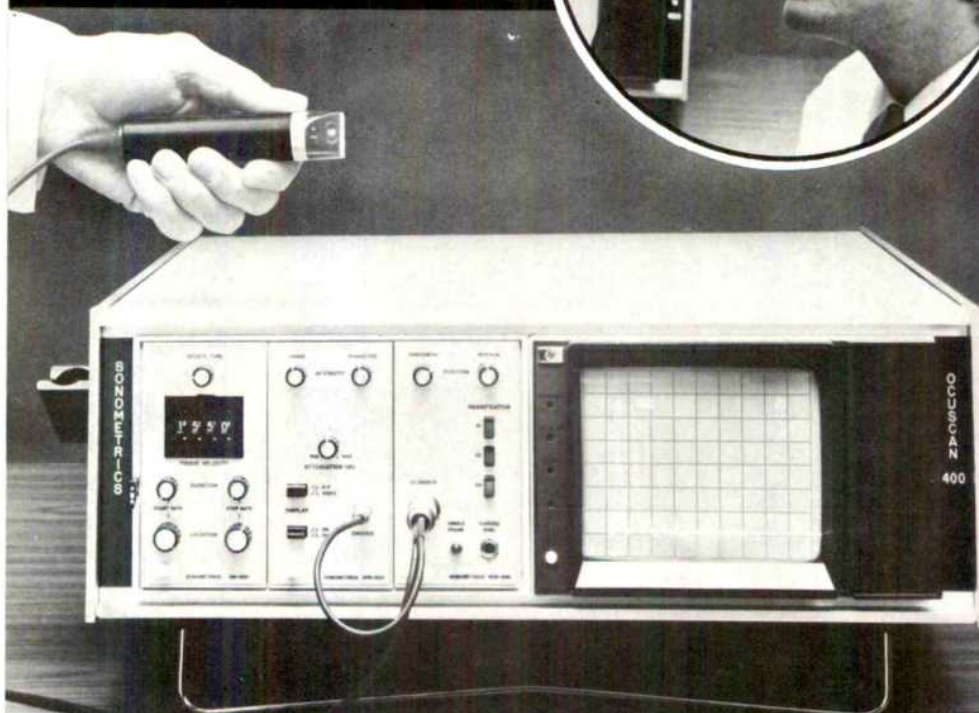
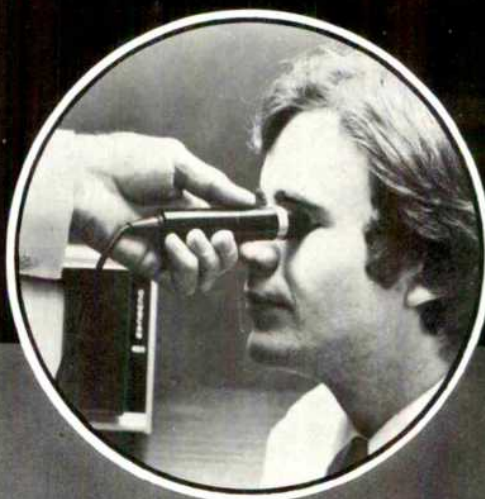
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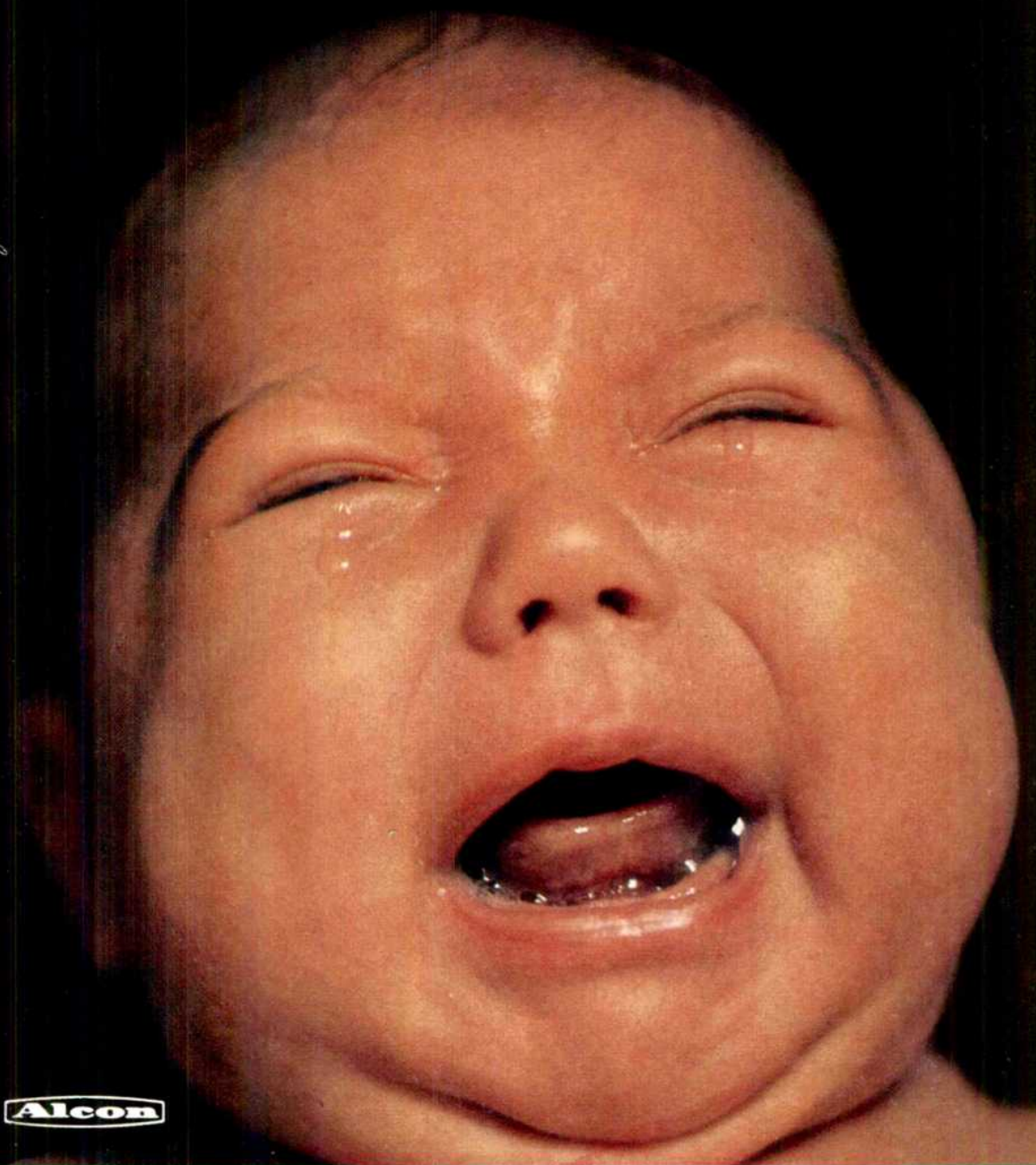
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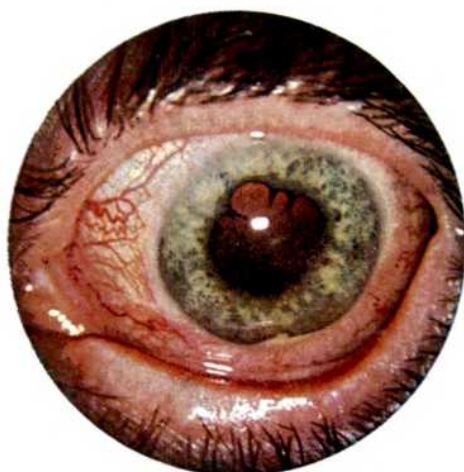
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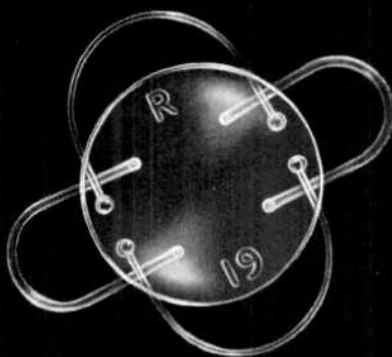
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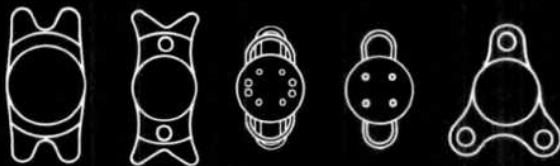


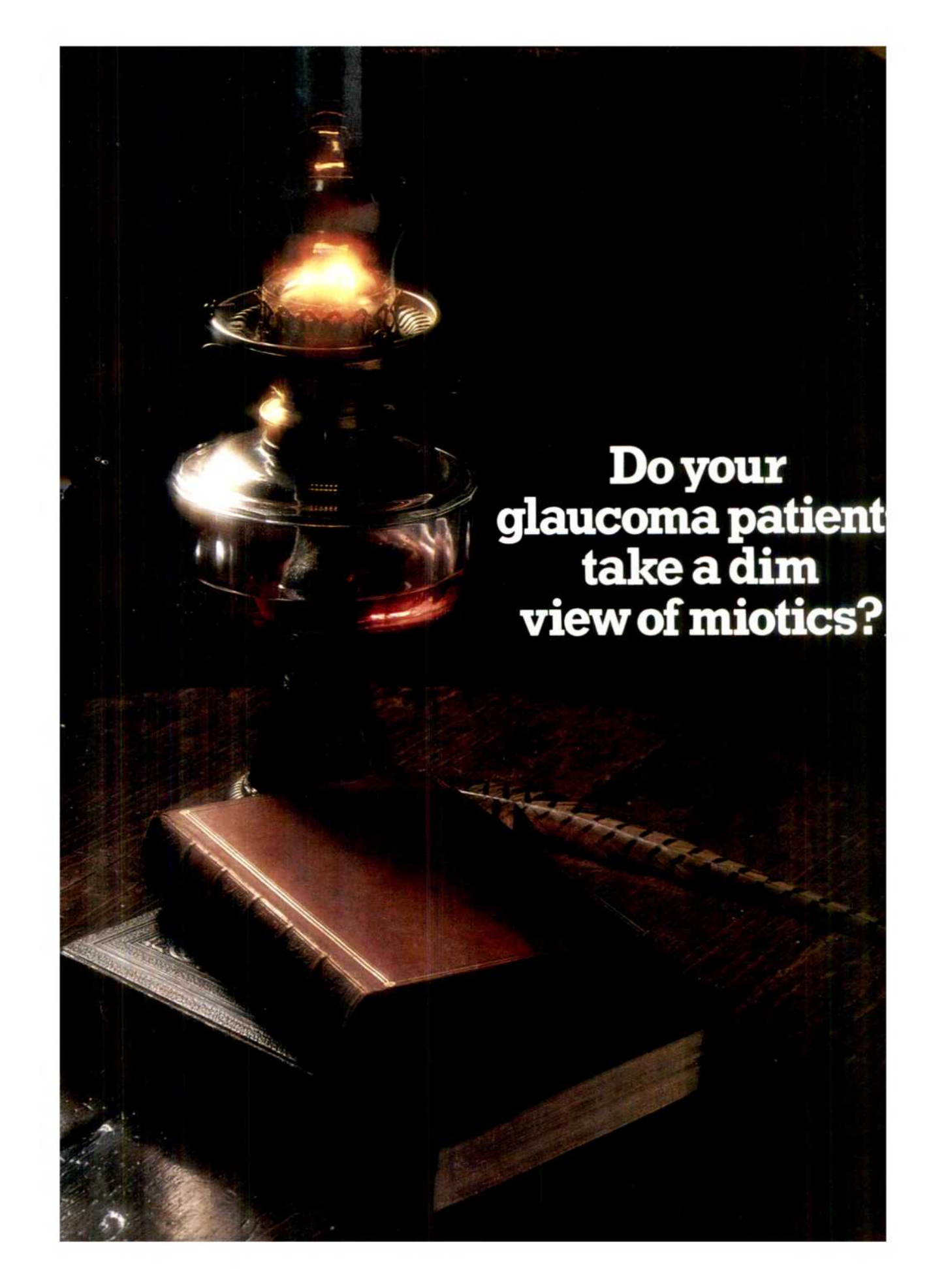
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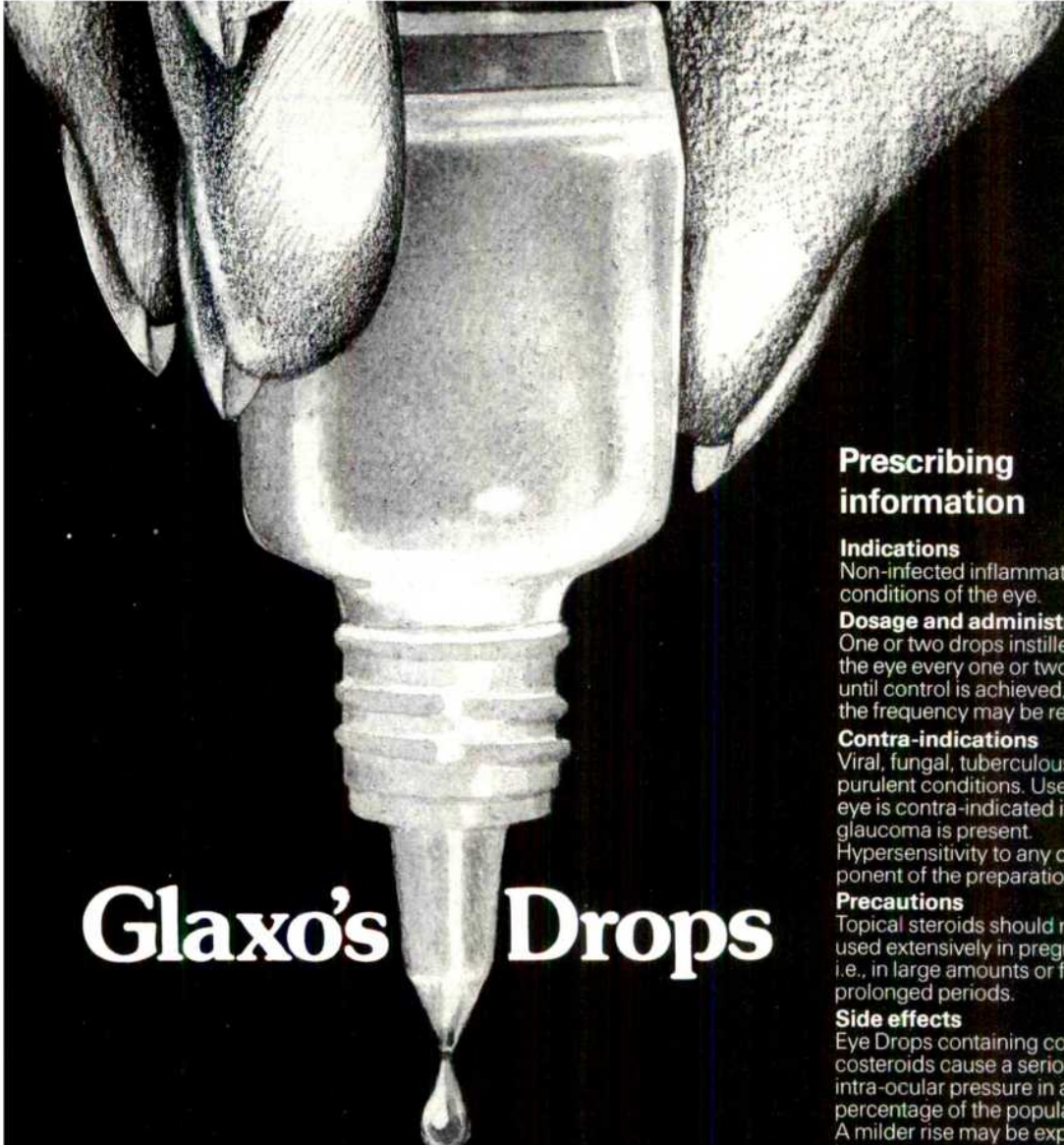
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Editorial: Photogrammetry of the optic disc

Research into methods of clinical examination and early detection of chronic simple glaucoma is once more shifting its emphasis towards new techniques for the testing and recording of visual fields. In the early 1970s the pendulum swung well away from these subjective forms of visual assessment towards a more objective approach, and interest centred around the examination of the pathological optic disc, its local vasculature and related nerve fibre layer. During this period the techniques of photogrammetry received a certain amount of consideration in the quantitative evaluation of optic disc cupping.

Photogrammetry may be defined as the science or art of obtaining reliable measurements by means of photography. It depends on accurate instrumentation and recording devices and is the province of the map-maker, the surveyor, the geologist, and the space scientist. It already has several applications in medicine, including orthodontics, plastic surgery, and radiology. It is a science because it has its foundations in applied mathematics aided by the use of sophisticated apparatus and modern computerised techniques. It remains an art because in many instances it still relies on the skill and judgment of the individual observer making measurements.

The accurate assessment of the depth of the optic disc and the extent of pathological cupping has been the goal of glaucoma workers for many years, and its value in early detection was re-emphasised in 2 recent Doyne memorial lectures.^{1,2} Any method that measures changes of optic disc volume would prove very helpful to our understanding of the pathogenesis of disc cupping and would also serve as a useful index of the progress of glaucoma and its response to therapy.

The work of Armaly³ on cup/disc ratios and subsequent attempts to apply quantitative measurements to disc cupping coincided with the rebirth of interest in stereoscopic fundus photography that was stimulated by the development of the stereoscopic fundus camera by Donaldson⁴ and the image separator by Allen and coworkers.⁵ Several authors applied the techniques of photogrammetry to 3-dimensional photographs of the optic disc using the Allen image separator to provide stereoscopic pairs,⁶⁻⁸ but this method proved too inaccurate because of the constant difficulty in maintaining a fixed stereoscopic base between the separate exposures. It was soon supplanted by simultaneous

stereophotography using twin-prism devices initially⁹⁻¹¹ and later employing the Donaldson stereoscopic fundus camera when it became more generally available¹² (and see Rosenthal *et al.* in this issue). It was possible with these instruments to take simultaneous stereoscopic photographs of the optic disc and thus eliminate many of the errors that featured in previous forms of measurement.

The problems associated with the actual recording of disc depths from stereophotographs, however, still remain. Until recently the photogrammetrist, examining stereoscopic pairs with optomechanical stereoplotting machines or using digital methods, had no reliable technique for calibrating the readings in terms of the geometry of the optic disc or of verifying the accuracy of the calculated disc cup volumes, and the methods described in this issue by Rosenthal *et al.* are a welcome and necessary attempt to improve on this accuracy. Comparative and sequential studies on the evolution of disc changes are now possible, but continued research is needed into patients with glaucoma to evaluate these methods' true significance.

The main disadvantage of stereophotogrammetry is that it is a laborious and time-consuming procedure requiring expensive equipment and experienced observers to undertake stereoplotting—it may be necessary to take several hundred readings from a single stereoscopic pair of disc photographs—and the cost and time involved in using the technique are prohibitive in the conventional clinical situation.

Other simpler nonstereo methods of estimating disc depth and the extent of cupping do exist. They include light-sectioning techniques with multiple-slit illumination of the disc in order to display its contours,^{13,14} and qualitative assessments may be made with a stereoscopic comparator¹⁵ or by the technique of stereochorescopy.¹⁶ But all these methods lack sufficient accuracy to allow reproducible measurements to be made.

If optic disc photogrammetry is to prove valuable in the clinical assessment of disc cupping, it must be developed into a simple and relatively inexpensive technique that can provide accurate quantitative as well as qualitative measurements of the various 3-dimensional parameters that characterise the developing glaucoma cup. Perhaps some of the new advances in computer technology will facilitate the actual measurements themselves and replace the work of the individual stereoplotter, but until these requirements can be met the technique is unlikely

to remain anything more than a lengthy and laborious research investigation.

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Photogrammetry experiments with a model eye

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SUMMARY Digital photogrammetry was performed on stereophotographs of the optic nerve head of a modified Zeiss model eye in which optic cups of varying depths could be simulated. Experiments were undertaken to determine the impact of both photographic and ocular variables on the photogrammetric measurements of cup depth. The photogrammetric procedure tolerates refocusing, repositioning, and realignment as well as small variations in the geometric position of the camera. Progressive underestimation of cup depth was observed with increasing myopia, while progressive overestimation was noted with increasing hyperopia. High cylindrical errors at axis 90° led to significant errors in cup depth estimates, while high cylindrical errors at axis 180° did not materially affect the accuracy of the analysis. Finally, cup depths were seriously underestimated when the pupil diameter was less than 5.0 mm.

A digital photogrammetric technique has been used to quantitate optic nerve head cupping employing stereophotographs.¹ Comparative studies indicated that the most reproducible results were obtained when simultaneous stereophotographs were taken with the Donaldson stereoscopic fundus camera.² Since there is no accurate method for comparing the actual geometry with the photogrammetric estimates in the human eye, we thought it would be useful to use a model eye in which a cup with known dimensions could be photographed and analysed. In addition experiments were undertaken to determine the impact of photographic and ocular variables on the photogrammetric estimates of a known cup depth in photographs taken with the Donaldson stereo fundus camera.

Materials and methods

MODEL EYE

A Zeiss model eye was modified by adding an optic cup with an adjustable depth (Figs. 1a and b). This cup was created by drilling out the optic disc and inserting a nylon piston in the resulting hole. The diameter of the cup equalled the diameter of the disc. The piston was painted white to simulate the disc, and radial stripes were overlaid to simulate vessels (Fig. 2). The piston's position was controlled with a precision micrometer so that optic cups of varying depths could be achieved (Fig. 1b). The model eye specifications are presented in Table 1.

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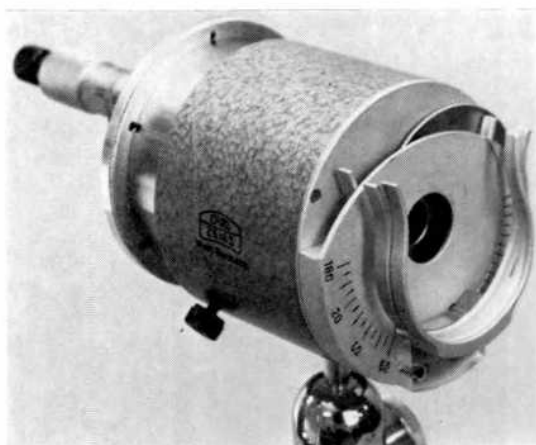


Fig. 1a Zeiss model eye (front view).



Fig. 1b Zeiss model eye (back view).

CAMERA

The Donaldson stereoscopic fundus camera was used to take all the disc stereophotographs.³ The approximate specifications of the Donaldson stereoscopic fundus camera used in this study are displayed in Table 2.

PHOTOGRAPHIC PROCEDURE

The modified model eye was mounted securely on the headrest ring of the Donaldson fundus camera with an aluminium bar and clamp. Stereopairs were taken in the usual way after centring the optic disc in the camera's viewfield. Uniform illumination of the nerve head was obtained by shifting the camera horizontally and vertically until the illumination light entered the model eye's pupil in a symmetric configuration. Spurious reflections were eliminated and exact focus was achieved before photographs were taken.

All photographs were taken with the superior

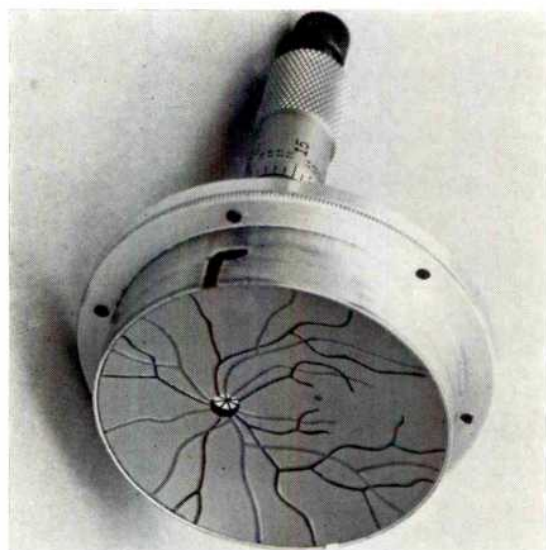


Fig. 2 Simulated optic disc and retina in Zeiss model eye.

Table 1 Zeiss model eye parameters

Focal length of lens:	50 mm
Optic cup diameter:	3.75 mm
Cup depth:	Variable from 1 mm cup elevation to 9 mm cup depression
Pupil size:	Variable from 4–8 mm
Refractive error:	Variable from –5 myopia to +6 hyperopia
Nominal cup depth:	1.27 mm used for all experiments, except the one in which variations in depth were measured

Table 2 Specifications and measurements of Donaldson stereofundus camera

Stereobase:	2.50 and 2.875 mm
Focal length of camera:	8.67 mm (at 6 times camera magnification)
Focal length of objective lens:	50 mm (corresponds with that of model eye)
Focal length of relay lens:	95 mm (approximate)
Image magnification on film:	1.70 (at 6 times camera magnification)

and inferior portions of the retinal surface in best focus. Accordingly, the nerve head vessels tended to go out of focus on the deepest cups. The nominal cup depth was set at 1.27 mm for studying most of the variables. The retina-to-film magnification was approximately 1.7. Stereobase plates with 4.5 and 5.0 mm apertures (5.0 and 5.75 mm centre-to-centre separation respectively) were used.

Kodachrome II film was used for all the photographs, and the resulting pictures were hand mounted in 2 inch × 2 inch (5 × 5 cm) slides.

VARIABLES STUDIED

Cup depth. The depth of the cup was varied by repositioning the micrometer so that depths varying from 0.00 mm to 3.81 mm in 0.64 mm increments were obtained.

Pupil size. Extra positions in the pupil wheel were drilled yielding pupil sizes of 4–8 mm in 1 mm increments.

Refractive error. Hyperopia and myopia of 5 dioptres in 1/2 dioptre increments were simulated by moving the retinal surface fore and aft respectively relative to the model eye's lens. Stereopairs were taken at 1/2 dioptre intervals to ensure a well defined curve of measurement error versus refractive error. Astigmatism was simulated by placing both plus and minus cylindrical lenses of 1 and 2 dioptres at both 90° and 180° in the model eye's lens holder.

Refocusing/realigning/repositioning effects. Stereopairs were taken of the model eye after the following manoeuvres were performed either separately or in combination: refocusing, realigning, and repositioning of the fundus camera.

Elevational and azimuthal effects. Stereophotographs were taken of the model eye after rotating the fundus camera from the determined centered position 1/4 and 1/2 disc diameters in both the horizontal and vertical directions.

Horizontal and vertical translational effects. Stereophotographs were taken of the model eye after the fundus camera was moved 1 and 2 mm right and left and up and down from its nominally centred position.

DIGITAL PHOTOGRAMMETRIC PROCEDURE

The developed and mounted stereopairs were digitised with an electronic film scanner. The recording matrix used was 256×256 pixels with a pixel-to-pixel spacing of $10 \mu\text{m}$. This matrix and spacing limited the scanning operation to $1/3$ of the disc area. Accordingly the superior portion of the optic disc and the adjoining portion of the retinal surface were selected for digitisation.

A new program, MODEL, was abstracted from our traditional one, STEREO. Since a full-height map was unnecessary, this algorithm made a single determination of the absolute height of the optic cup relative to the retinal surface.

The depth sensitivity was defined as the smallest change in cup depth which can be confidently detected by the procedure. This distance is directly proportional to the pixel spacing and is a function of the mask geometry and the focal lengths of the camera and the model eye. In the present study the depth sensitivity was 0.105 mm and 0.120 mm when the 5.75 mm and 5.00 mm masks were respectively employed.

Results

Measured vs. actual depth. In order to determine how accurately the photogrammetric procedure measures different cup sizes, stereopairs were taken at various cup depths with no changes in the fundus camera conditions. Three measurements were made at each cup depth. The eye was set at emmetropia, and the 5.75 mm mask was used throughout the photographic session. Table 3 shows how the photogrammetric procedure measures known variations in cup depth, while Fig. 3 graphically displays these results.

OPTIC VARIABLES

Pupillary diameter. To determine the impact of pupil size on cup depth measurements 3 stereopairs were taken of the nerve head of the model eye at different pupil diameters with the fundus camera left in fixed position. In this set of photographs the eye was set at emmetropia and the 5.0 mm mask was employed, except at the 3 mm pupil, when the 5.75 mm mask was used.

Results are tabulated in Table 4 and displayed graphically in Fig. 4. Note that the measured depth of the optic cup decreased when pupil diameters were less than 5 mm . By means of the correction factor detailed in a previous communication⁴ a corrected cup depth is calculated for each pupil size and is included in Table 4. This corrected cup depth when pupil size was less than 5 mm is comparable to the actual depth.

Refractive error. Three stereophotographs were taken of the optic nerve head of the model eye at varying degrees of hyperopia and myopia. For all the photographs the 5.0 mm mask was employed. To correct for refraction effects a theoretical analysis was undertaken, and the formulas produced from this analysis⁴ were used to correct the measured cup depths. Table 5 displays the effect of refractive error on cup depth measurements.

Note that the measured cup depth decreases dramatically with increasing myopia and increases dramatically with increasing hyperopia. Fig. 5 shows graphically how the cup depth estimates change with alterations in refractive error when the Donaldson camera is used to photograph either the model eye or the human eye. The former curve

Table 3 Accuracy of photogrammetric procedure

Actual cup depth (mm)	Measured cup depth (mm) Mean $\pm$ SD, $n=3$
0.00	0.26 ± 0.07
0.64	0.63 ± 0.02
1.27	1.26 ± 0.11
1.90	1.98 ± 0.07
2.54	2.55 ± 0.04
3.18	3.13 ± 0.11
3.81	3.44 ± 0.27

Depth sensitivity = 0.105 mm .

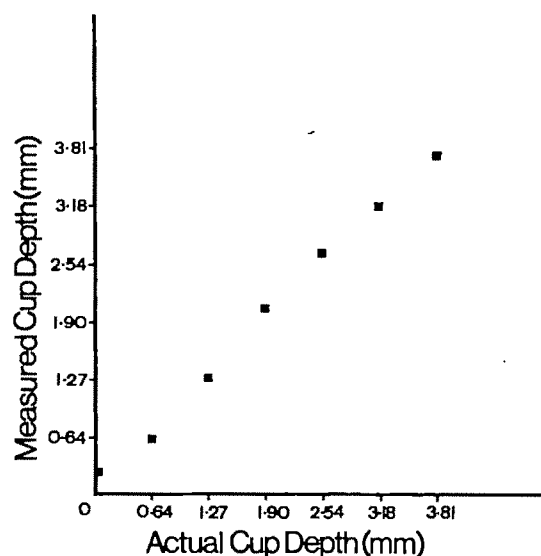


Fig. 3 Comparison of measured cup depth by the photogrammetric procedure with actual cup depth of the Zeiss model eye.

is determined from these experiments, while the latter curve is established from theoretical considerations.⁴

Astigmatism. One stereopair was taken of the optic nerve of the model eye after cylindrical lenses were mounted in the lens holder of the model eye. The 5.0 mm mask was used in the camera. Table 6 details the results of the photogrammetrically measured cup depths as compared with the actual depths.

Though only one stereopair was taken with each astigmatic error, it appears that high horizontal and vertical cylinders affect cup depth estimates differently. High positive vertical axis cylinders appear to underestimate cup depth, while high negative vertical axis cylinders seem to have the opposite effect of overestimating the cup depth. Lower

Table 4 Cup depth and pupil size

Pupil diameter (mm)	Actual cup depth (mm)	Measured cup depth (mm) $n = 3$	Corrected cup depth (mm)
3	1.27	0.70	1.20
4	1.27	1.05	1.31
5	1.27	1.28	1.28
6	1.27	1.30	1.30
7	1.27	1.25	1.25
8	1.27	1.27	1.27

Depth sensitivity = 0.120 mm except with 3 mm pupil, where it equals 0.105 mm.

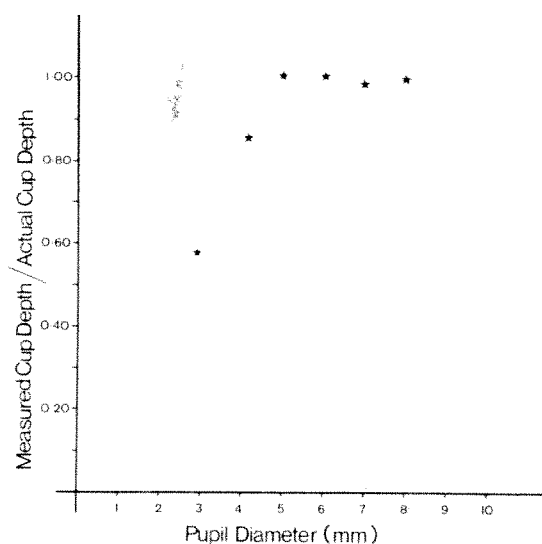


Fig. 4 Effect of pupil diameter on measured cup depth in the Zeiss model eye.

Table 5 Effect of refractive error on cup depth measurements

	Refractive error (dioptries)	Actual cup depth (mm)	Measured cup depth (mm) $n = 3$	Corrected cup depth (mm)
Myopia	5.0	1.27	0.48	0.92
	4.5	1.27	0.48	0.86
	4.0	1.27	0.24	0.40
	3.5	1.27	Not done	Not done
	3.0	1.27	0.48	0.70
	2.5	1.27	0.72	1.00
	2.0	1.27	0.60	0.75
	1.5	1.27	0.72	0.80
	1.0	1.27	0.84	0.93
	0.5	1.27	0.96	0.99
Emmetropia	0	1.27	1.20	1.20
Hypertropia	0.5	1.27	1.20	1.05
	1.0	1.27	1.32	1.12
	1.5	1.27	1.20	0.95
	2.0	1.27	2.04	1.53
	2.5	1.27	1.80	1.28
	3.0	1.27	1.92	1.28
	3.5	1.27	2.28	1.46
	4.0	1.27	2.76	1.66
	4.5	1.27	2.28	1.32
	5.0	1.27	2.40	1.29

Depth sensitivity = 0.120 mm.

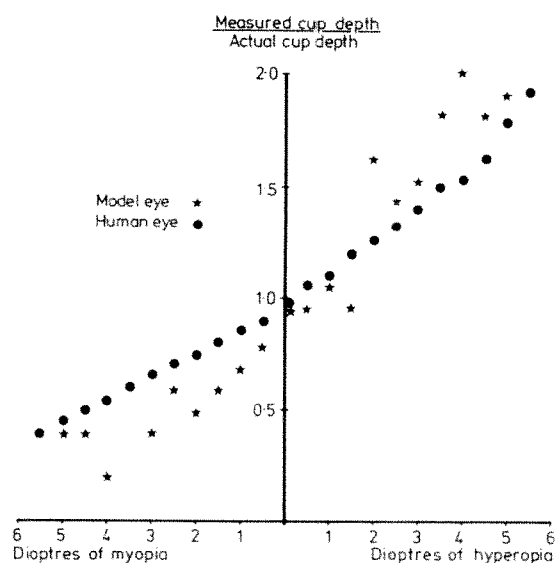


Fig. 5 Effect of refractive error on measured cup depth in the Zeiss model eye.

Table 6 Cylindrical errors

Cylinder		Cup depth	
Dioptres	Axis (degrees)	Actual cup depth (mm)	Measured cup depth (mm) <i>n</i> = 1
Emmetropia		1.27	1.20
+2.0	90	1.27	0.84
+1.0	90	1.27	1.20
-1.0	90	1.27	1.32
-2.0	90	1.27	1.44
+2.0	180	1.27	1.20
+1.0	180	1.27	1.32
-1.0	180	1.27	1.20
-2.0	180	1.27	1.32

Depth sensitivity = 0.120 mm.

Table 7 Effect of refocusing, realignment, and repositioning on cup depth of model eye

Type of camera adjustment	Actual cup depth (mm)	Measured cup depth (mm) Mean $\pm$ SD, <i>n</i> = 5
No adjustments*	1.27	1.27 $\pm$ 0.086
Camera refocused*	1.27	1.21 $\pm$ 0.092
Camera realigned**	1.27	1.23 $\pm$ 0.087
Camera realigned and refocused**	1.27	1.28 $\pm$ 0.079
Camera repositioned, realigned, and refocused**	1.27	1.20 $\pm$ 0.079

*Depth sensitivity = 0.105 mm.

**Depth sensitivity = 0.120 mm.

cylindrical errors do not seem to alter the accuracy of the analysis. Neither high nor low horizontal axis cylinders appear to have a systematic effect on the photogrammetric estimation of cup depth.

PHOTOGRAPHIC VARIABLES

Realignment, refocusing, repositioning. Five stereopairs were taken of the model eye optic disc after the following manoeuvres were performed with the fundus camera: refocusing, realignment, realignment and refocusing, and finally repositioning, realignment, and refocusing. The first set of photographs was taken with the 5.75 mm mask, while the latter 3 groups of photographs were taken with the 5.0 mm mask. The eye was set at emmetropia for all the photographs. Table 7 details the results of the digital photogrammetric analyses. No significant alterations in cup depth measurements were produced by these manoeuvres.

Elevational and azimuthal effects. One stereopair of the model eye disc was taken after rotating the fundus camera by 1/4 disc diameter (1 step rotation)

and 1/2 disc diameter (2 step rotation) in both horizontal and vertical directions. All photographs were taken in the emmetropic position using the 5.75 mm mask. Poor agreement between actual and measured cup depth occurred as a result of these manoeuvres. Table 8 displays the results of the digital photogrammetric analyses.

Horizontal and vertical translational effects on optic cup depth. One stereopair was taken of the model eye disc after the fundus camera was moved right and left and up and down by 1 and 2 mm from the nominally centered position. The photographs were taken in the emmetropic eye with the 5.75 mm mask. Table 9 displays the results of these analyses. Though only one stereopair was analysed, the estimated depths with horizontal adjustments seemed to be more erroneous the further the camera was off centre. With vertical translational movements

Table 8 Elevational and azimuthal effects on estimated cup depth

Type of angular camera adjustment	Actual cup depth (mm)	Measured cup depth (mm) <i>n</i> = 1
Camera in central position	1.27	1.37
Camera rotated right by 1 step	1.27	1.26
Camera rotated right by 2 steps	1.27	1.16
Camera rotated left by 1 step	1.27	1.16
Camera rotated left by 2 steps	1.27	1.37
Camera returned to central position	1.27	1.37
Camera rotated upward 1 step	1.27	0.95
Camera rotated upward 2 steps	1.27	1.37
Camera rotated downward 1 step	1.27	1.58
Camera rotated downward 2 steps	1.27	1.68

Depth sensitivity = 0.105 mm.

Table 9 Effect of horizontal and vertical translational movements on estimated cup depth

Type of translational camera adjustment	Actual cup depth (mm)	Measured cup depth (mm) <i>n</i> = 1
Camera in centered position	1.27	1.26
Camera shifted right 1 mm	1.27	1.26
Camera shifted right 2 mm	1.27	0.95
Camera shifted left 1 mm	1.27	1.37
Camera shifted left 2 mm	1.27	1.68
Camera returned to central position	1.27	1.37
Camera shifted upward 1 mm	1.27	1.47
Camera shifted upward 2 mm	1.27	0.95
Camera shifted downward 1 mm	1.27	1.37
Camera shifted downward 2 mm	1.27	1.26

Depth sensitivity = 0.105 mm.

the errors in measured cup depth did not appear to be associated with the amount of camera movement.

Discussion

The digital photogrammetric measurements of cup depth in the model eye accurately approximated the actual cup depth except with very deep cups. The larger error on the deeper cups is probably due to poor focus on the vessels at the cup bottom, since the photographs were taken using the retinal surface as the plane of best focus for the photographer. This dilemma might also be encountered in the human eye, in which the cup is so deep that out-of-focus photographs result. It is extremely difficult to overcome this problem. Hence certain limitations on the usefulness of digital photogrammetry in patients with advanced glaucoma and extremely deep cups are created.

The chief source of error in the cup depth estimates resulted from the finite depth sensitivity which in turn derives from the finite pixel spacing of the film digitiser. The depth sensitivities of 0.105 and 0.120 mm are much poorer than those we are accustomed to when analysing the disc photographs of patients. This reduction in depth sensitivity results from the quadratic dependence of the depth sensitivity on the model eye's focal length, which is approximately 3 times that of the human eye. Since the model eye geometry is 3 times that of the human eye, the poorer depth sensitivity proved acceptable in the cup depth analysis, and changes of 0.53–0.60 mm could be easily detected with the above sensitivities. What changes will be clinically detectable and significant in patients with chronically elevated intraocular pressure are at present unknown. If one interpolates these data to the human eye, changes of approximately 59–67 μm can easily be measured. What this change represents in terms of cup contour is still a matter of speculation.

Other differences exist in the optics of the model and human eyes. Most notably, the pupil is in front of the cornea in the model eye, and ametropia is simulated solely by moving the retina rather than by a combination of axial length and corneal curvature. Moreover, we appreciate the fact that the optic cup of the Zeiss model eye is not a perfect facsimile of the human optic nerve head and cup. The absolute symmetrical cylindrical contour with the flat floor to the cup without the subtle topographical contours of the human cup make it a less than perfect model. However, it did provide a means of studying the photogrammetric accuracy with *known* cup depths.

The errors induced in cup depth measurements with reduction in pupil diameter below 5 mm indicate that it is important to measure and record

the actual diameter of the patient's pupil during stereophotography. Pupils 4 mm and smaller will not permit either adequate stereophotography with the Donaldson camera or accurate digital photogrammetric evaluation. We must be aware that visit-to-visit variations in pupil size can produce false impressions of progressive change in cup size. If the diameter of the pupil is less than 5.0 mm, correction factors might have to be used to adjust for alterations in cup parameters induced by the pupil size.

The underestimation and overestimation of cup depth with myopia and hyperopia respectively is a more serious problem in terms of accuracy of absolute measurements. We must therefore take them into account when measuring cup depth. High hyperopia will lead to excessively large estimates of cup depth, while high myopia will lead to excessively small estimates. However, such incorrect values will not produce false impressions concerning progressive changes in cup depth or contour. Hence the ability of digital photogrammetry to detect progressive or relative changes in cup topography with chronic elevations in intraocular pressure is not altered by the patient's refractive error. Finally, we must also bear in mind that error in the cup depth measurement tends to increase with increasing myopia.

The addition of a cylinder to the model eye introduces an error into the measurement of cup depth. This error is noted only when the cylindrical axis is at 90° . With a cylinder axis at 180° the error is within the limits of the analysis. Moreover, the introduced error is related to the power of the cylinder, i.e., a plus cylinder causes an underestimation of cup depth and a minus cylinder causes overestimation. An explanation for these observations is as follows. The cylinders together with the camera lens in effect form a simple Galilean telescope, but they produce linear magnification or reduction in only one meridian, namely, the meridian perpendicular to the axis. This distortion produces an apparent (but not real) change in the cup depth. In this system a plus cylinder axis 90° in the Galilean system will magnify linearly along 180° . Since the depth is measured by parallax using points along the horizontal axis, it will appear smaller relative to this elongation of the horizontal axis by the plus cylinder axis 90° . The converse would be true with the minus cylinder axis 90° . One would not expect cylinders axis 180° to alter the computer's depth analysis, since they will not magnify the points along the horizontal axis.

We feel confident that simple photographic manoeuvres, for example, refocusing, realignment, and repositioning, should not materially affect the

accuracy of the digital photogrammetric technique. However, more complex manoeuvres such as elevational and azimuthal rotations of the camera as well as horizontal and vertical translational movement can alter the accuracy of the technique. The complex manoeuvres of elevation and translation are very difficult to perform with the Donaldson camera and particularly in this situation, where a model eye is securely mounted to the headrest. However, in a clinical setting (and with other types of fundus cameras) the equivalent of these complex manoeuvres may be performed by the patient through either faulty positioning in the headrest or faulty fixation. Such malalignments of the camera system with the eye's axis, are therefore possible in the clinical setting, and great precaution should be taken to avoid them.

Since the photogrammetric procedure in the model eye examines only a small region of the optic disc and border, averages measurements over only 2 depth planes, and uses an artificial fundus pattern, the accuracy of cup depth measurement from photogrammetric analyses of optic cups in the human eye cannot be intuitively expected. Methods

of determining actual cup depth in the human optic nerve head must be developed so that comparison with photogrammetric estimates can be undertaken before one can feel confident that digital photogrammetric estimates of cup depth from stereophotographs of human optic cups are accurate.

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Microepithelial cysts observed in extended contact-lens wearing subjects

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SUMMARY After 18 weeks of a controlled comparative study of extended contact lens wear a male subject presented with ocular symptoms. Microepithelial cysts were observed in both eyes and, after examination, in the eyes of 44 other participating patients. The cysts have been photographed and the rate of recovery monitored.

Microepithelial cysts have been reported in a number of ocular disorders¹⁻³ and occasionally observed in differing types of contact lens wear. In a comparative controlled study, now reported, a high incidence of such cysts was encountered after approximately 6 months of extended soft contact lens wear.

Material and methods

A group of 75 Caucasian volunteers who came within a previously determined acceptance profile were randomly divided into 3 groups of 25 subjects each. Two groups were fitted with Sauflon PW lenses (Contact Lenses Manufacturing), while the third group remained unfitted with contact lenses and acted as controls. One group of subjects wore their contact lenses without removal and without recourse to proprietary cleaning agents. The second lens wearing group had their lenses removed at 4-weekly intervals and cleaned with Monoclen C40 (Contact Lens Manufacturing). The subjects were examined at 2, 4, 6, and 8 days; 2, 3, and 4 weeks; and 2, 3, 4½, and 6 months, and a variety of subjective information and data were collected.

Results

At the eighteenth week of the study a male subject presented with symptoms of discomfort in the right eye. The conjunctiva was mildly congested and showed evidence of superficial epithelial disturbance in the lower nasal quadrant which stained with 2% sodium fluorescein. Visual acuity was reduced to 6/7.5 from a previously corrected 6/5. The contact lens previously worn on the eye was observed to be

damaged, and it was considered that the ocular signs and symptoms were consistent with the lens damage. However, on examining the eye a number of small, discrete, unstained epithelial cysts were observed in the lower portion of the cornea. After this observation 6 further subjects were examined and all showed the presence of similar bodies. As a consequence all further contact-lens wearing subjects were examined and a number of slit-lamp photomicrographs taken with the aid of a Holden/Zantos attachment to a Nikon Photo-Slip Lamp. Examples of the photographed appearance are shown in Figs. 1 and 2. Of 45 contact-lens wearing subjects 44 showed evidence of epithelial cysts, while the remaining subject developed cysts 2 weeks after contact lens wear had ceased. However, the severity of cysts varied, and for the purposes of the study the appearance of the cysts was ranked at 5 levels. Although the presence of cysts was not considered to be particularly serious, their presence in all subjects caused the study to be abandoned and lens wear was stopped. After lens removal the patients were monitored for recovery over the next 20 weeks. The ranked severity of cysts and recovery rate are tabulated in Table 1.

Discussion

The widespread incidence of microepithelial cysts was an unexpected complication to extended soft contact-lens wear. Brown and Lobascher⁴ reported cysts to occur in aphakic subjects wearing Permalens. More recently Josephson⁵ has reported a single patient presenting with cysts from an unidentified form of extended contact-lens wear. The cysts in the present instance occurred in almost all subjects after approximately the same period of lens wear. With the exception of the first subject, who had a damaged lens, the patients were asymptomatic and

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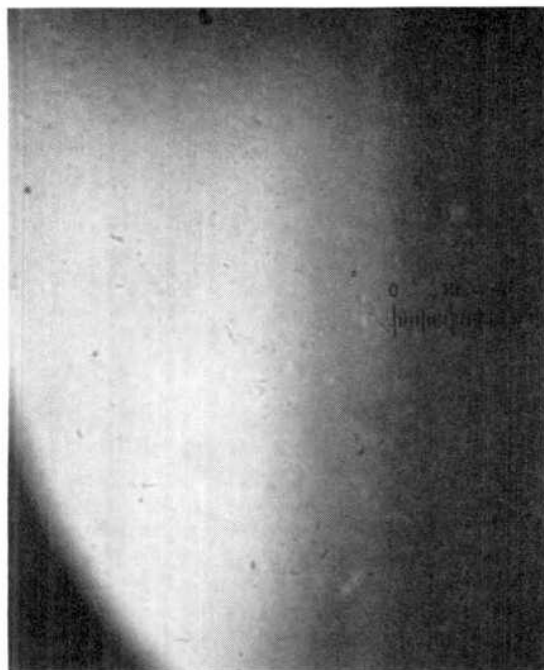


Fig. 1 Microepithelial cysts photographed with a Holden/Zantos attachment on a Nikon photo slit-lamp. Ten scale divisions = 140 μ m.

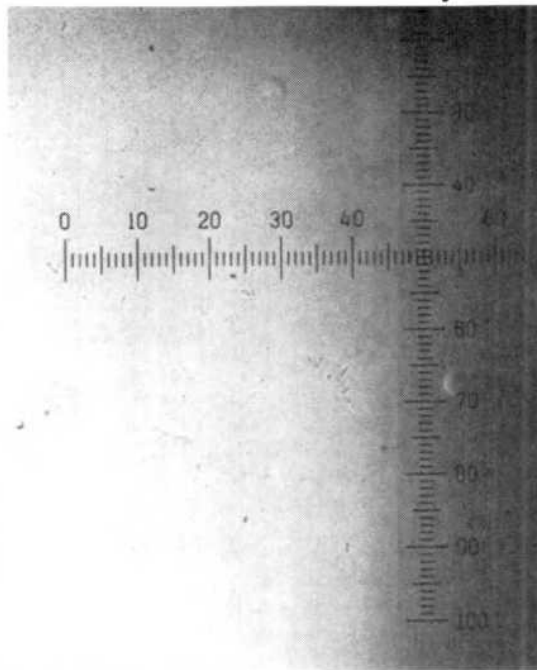


Fig. 2 Microepithelial cysts photographed with a Holden/Zantos attachment on a Nikon photo slit-lamp. Ten scale divisions = 140 μ m.

showed no other ocular signs. The cysts appeared to range in size between 10 and 90 μ m in diameter and were most easily viewed by retroillumination. The recovery time averaged 10 weeks and thus was considerably beyond the life cycle of individual epithelial cells, suggesting some form of attachment, possibly to Bowman's membrane.

The aetiology of microepithelial cysts in the cystic disorders has been well documented.^{6,7} In the present instance the cysts observed in extended contact-lens wearing patients, and in patients having Meesman's dystrophy, appear to have the closest clinical resemblance.

Of themselves the cysts may not be particularly serious. However, Ruben (personal communication) has suggested that a proportion may progress to

subepithelial fibrillar changes with eventual involvement of Bowman's membrane and corresponding reduction of vision, which would clearly be unacceptable in cosmetic contact-lens wear.

We acknowledge the support of the Medical Research Council and Contact Lenses Manufacturing in carrying out this work.

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Table 1 Ranked severity of microepithelial cysts and recovery rate in weeks

Ranked severity	1	2	3	4	5
Number of patients	33	9	2	1	0
Average recovery time (weeks)	8.9	8.9	12	11	0

Ranking criteria. Area of cornea covered by cysts: (1) Up to 20% of total corneal surface, (2) 21%-40%, (3) 41%-60%, (4) 61%-80%, (5) >80%.

West Indian punctate keratopathy in a Caucasian

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SUMMARY We present a patient with the picture of corneal white spots, very similar in morphology to those described in native West Indians, occurring here in a Caucasian. Their aetiology remains obscure.

The case is reported of a female Caucasian with white corneal spots described previously only in native West Indians. We believe this to be the only report of this finding in a Caucasian.

Case report

A 41-year-old white female presented to us in October 1978 with the complaint of intermittent redness and grittiness of both eyes for the previous 3 months. This had begun just before she had left Rhodesia at a time when she was nursing sick children, some with conjunctivitis. Her symptoms had responded favourably to betamethasone drops and she was currently asymptomatic.

She was born in Trinidad, West Indies, of white parents. Her schooling had been in Barbados from the age of 12 to 17, and from 18 to 24 years of age she had lived in England. From there she emigrated to Africa, where she lived until the age of 40. She had lived in Nyasaland for 18 months and had then moved to Rhodesia, initially in the Zambesi River Valley, later in the Low Veld, and then in Malsetter (East Rhodesia). She had lived among the black tribes as her husband was involved in tsetse fly control by aerial spraying. In August 1978 she returned to England.

She had filariasis diagnosed by blood examination a few years ago, and was treated with 2 courses of penicillin for primary syphilis on her return to England.

Examination of the patient showed the lesions to be confined to the left cornea. Both eyes were white, and there was no conjunctival reaction. The visual acuity, anterior chambers, irides, intraocular pressures, and fundi were all normal. The right cornea was normal.

The left cornea showed three small dense, white,

round, subepithelial spots clustered together in the inferonasal quadrant. The epithelium was intact and showed no staining areas with fluorescein or Bengal rose dyes. The deeper stromal layers and endothelium beneath the spots were normal. Corneal sensation was not impaired, and corneal thickness was in the normal range.

Figs. 1–3 show the spots. Each was approximately 0.2 mm in diameter, and high-power slit-lamp examination showed each dense area to have a coarse granular appearance, surrounded by a halo of stromal haze about as wide as the opacity itself.

Discussion

The dense white corneal spots described here in a Caucasian female appear to resemble those white spots in native West Indians reported by Rice *et al.*¹ As in their cases, the condition was a chance finding in a patient with symptoms seemingly unrelated to the presence of the spots. A diagnosis of West Indian spot was made before her place of birth had been established.

Unfortunately we have no electron microscopic confirmation of the identity of these spots.

The lesions in our case were confined to the interpalpebral cornea. In the paper of Rice *et al.*¹ trauma was mooted as a possible aetiological factor. Until now these lesions have been described only in West Indians, and in our patient also it is likely that the lesions were acquired during her domicile in the West Indies between birth and the age of 18 years. During that time it appears that she lived a life, in terms of exposure to trauma, no different from that of a British subject schooled in England.

Early ocular onchocerciasis may be seen as discoid or nummular opacities which are clear-cut, permanent, anterior stromal scars, usually in the interpalpebral zone and close to the limbus, and may be preceded or accompanied by a nonspecific

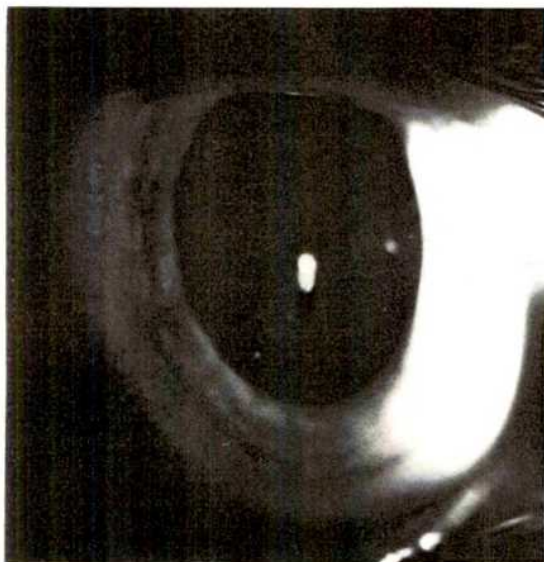


Fig. 1 West Indian spots, left cornea. Scleral scatter photograph of spots.

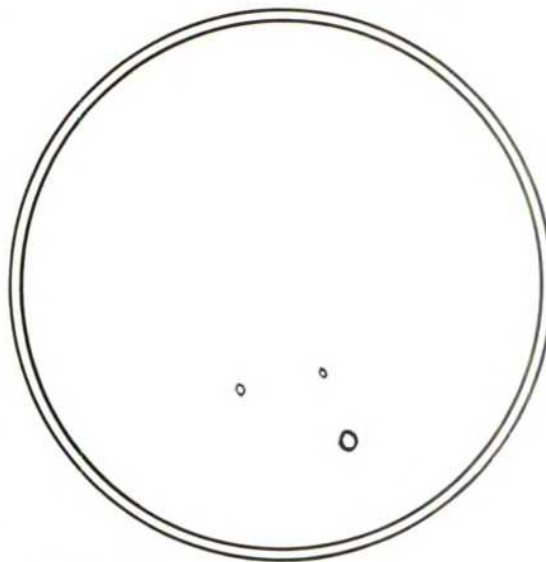


Fig. 2 Distribution of spots on cornea.

allergic type of conjunctivitis.² As our patient had not, so far as we know, lived in an endemic onchocerciasis zone, and as her filariasis was apparently diagnosed by a blood smear, it seems that she is unlikely to have been suffering from onchocerca infestation, and thus her corneal opacities cannot easily be attributed to this disease, nor did they have the morphology of onchocercal 'snow-flake' lesions.

There is also no corneal evidence of a syphilitic infection, and the appearances were not those of adenovirus or chlamydial keratitis.

Although the patient had been exposed to and had symptoms of conjunctivitis, the lesions were not active at the time of examination and did not vary in appearance over a period of 12 months.

The authors thank Mr D. Barbour for photographic preparation and Miss J. E. Sawyer for typing the manuscript.

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Fig. 3 Macrophotograph of West Indian spots ($\times 30$).

Branhamella keratitis

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SUMMARY Three cases of suppurative keratitis caused by *Branhamella catarrhalis* are described. Each presented as a localised stromal infiltrate in a previously scarred cornea. The condition responded to penicillin G and to gentamicin treatment.

Branhamella catarrhalis is a parasitic, commensal organism found in the normal nasopharynx¹ and conjunctiva^{2,3} which can exceptionally cause an acute or chronic catarrhal conjunctivitis that usually heals without serious sequelae when treated. It can also be a cause of suppurative keratitis, and we report 3 cases associated with this organism.

Material and methods

Corneal scrapings of the suppurative ulcerations were examined microscopically by Gram-stained smears. Scrapings were inoculated directly on to 2 blood agar plates. One plate was incubated aerobically and the other was incubated in an atmosphere of 10% CO₂. Robertson's cooked meat broth, tryptic digest broth, and thioglycollate broth were also inoculated. Sabouraud's agar and brain-heart infusion broth containing 100 µg/ml of chloramphenicol were inoculated for fungal isolation.

Micro-organisms were identified according to the methods outlined by Cowan and Steel.⁴ *Branhamella catarrhalis* is a Gram-negative diplococcus which was identified further on the basis of the following characteristics: oxidase positive, catalase positive, no haemolysis on blood agar, no production of pigment, no growth on MacConkey's agar, growth on nutrient agar, and weak growth when incubated at 22°C for 24 hours. No acid was produced from glucose, maltose, lactose, sucrose, or fructose. Nitrates were reduced to nitrites; indole and urease tests were negative.

Case reports

CASE 1

A 63-year-old male initially presented during 1970

with a herpetic dendritic keratitis which was treated with idoxuridine. He subsequently developed a disciform keratouveitis, and prednisolone phosphate 0.1% and atropine were administered. Two weeks later he returned with a central suppurative ulceration with hypopyon. Corneal scrapings grew a penicillinase-producing *Staphylococcus aureus* which was treated with topical methicillin and gentamicin. A topical steroid was administered when repeat cultures were sterile. Because of residual vascularisation and scarring an 8.1 mm penetrating keratoplasty with cataract extraction was performed 6 months later. Postoperatively vision improved to 6/12.

He remained asymptomatic until 1979, when he returned with a 2-day history of ocular pain and epiphora. Examination revealed vision reduced to light perception because of a central ulcerative suppurative keratitis with hypopyon. Microscopic examination of the corneal scrapings showed Gram-negative diplococci and inflammatory cells. Treatment was begun with subconjunctival gentamicin 20 mg, topical gentamicin 3 mg/ml 3-hourly, and atropine. Cultures grew a pure heavy growth of *Branhamella catarrhalis* on blood agar. Antibiotic sensitivity testing by the disc-diffusion method showed the organism to be sensitive to penicillin G, ampicillin, gentamicin, tetracycline, chloramphenicol, neomycin, and soframycin. The hypopyon and stromal infiltrate rapidly began to resolve. Repeat corneal scrapings on the third day of treatment showed no organisms microscopically, and cultures were sterile. Prednisolone phosphate 0.3% was begun and later changed to dexamethasone 0.1%, 4-hourly. The topical gentamicin was gradually decreased over a 3-week period. An indolent epithelial ulceration persisted, and subsequent viral culture was negative. A central tarsorrhaphy was performed, and the cornea slowly re-epithelialised with residual stromal scarring.

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CASE 2

A 9-year-old male was followed up from 1977 for asthma and vernal keratoconjunctivitis which had been treated with topical betamethasone and sodium cromoglycate. A pneumococcal corneal ulcer of the left eye occurred during 1978 which was treated with topical and systemic penicillin. Subsequent therapy included topical prednisolone phosphate 0.3% and sodium cromoglycate 3 times daily to both eyes.

He returned 1 year later with a 2-day history of a painful right eye. Examination revealed a vision of 6/60 with a 5.5-mm² elliptical stromal abscess of

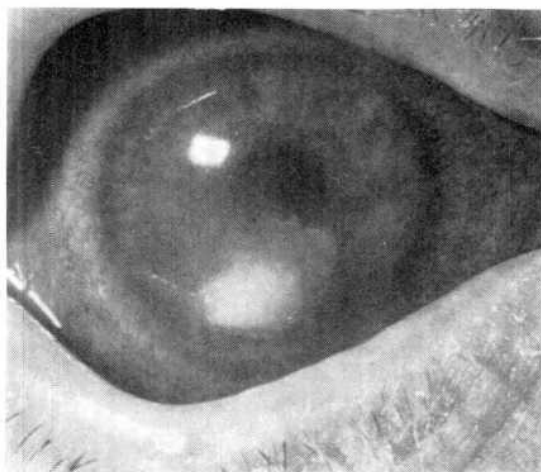


Fig. 1 Case 2. A suppurative stromal abscess is present within the inferior cornea in association with vernal conjunctivitis.

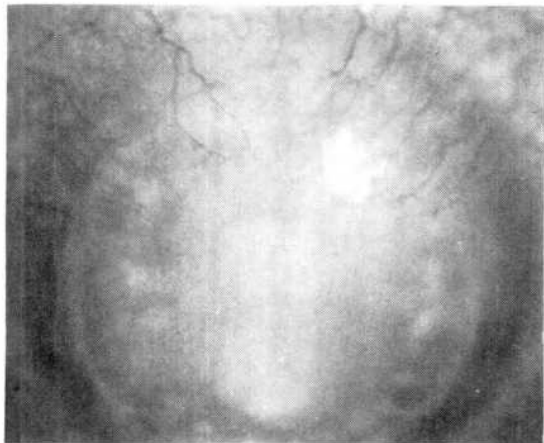


Fig. 2 Case 3. An oedematous corneal graft developed stromal infiltration with an underlying plaque on the endothelial surface.

the inferior cornea (Fig. 1). Gram staining of corneal scrapings showed many inflammatory cells, but no micro-organisms were seen. Treatment was begun with subconjunctival gentamicin 10 mg and penicillin G 250 000 units. Topical gentamicin and penicillin G were administered hourly and atropine 6-hourly. Cultures subsequently showed a pure moderate growth of *Branhamella catarrhalis*. Disc sensitivity testing showed the organism to be sensitive to penicillin G, ampicillin, gentamicin, tetracycline, chloramphenicol, neomycin, and soframycin. The gentamicin was then stopped, and treatment was continued with topical penicillin G. The stromal oedema and infiltrate rapidly began to resolve, and the penicillin dose interval was gradually increased. Acetylcysteine 10% and dexamethasone 0.1% were administered from the eighth day of treatment. Vision improved to 6/9 with a small residual stromal scar.

CASE 3

A 61-year-old female with recurrent ulcerative herpetic keratitis since 1966 subsequently developed stromal keratitis and was treated with topical prednisolone phosphate 0.5%. Progressive thinning resulted in a central descemetocoele requiring a 7-mm penetrating keratoplasty. A graft rejection occurred 5 months postoperatively, which was controlled with intensive topical steroid therapy. The steroid treatment was complicated by a herpetic geographic ulcer. Because of persistent stromal oedema an 8.5-mm keratoplasty was performed 9 months later. Stromal vascularisation and oedema developed despite topical steroid, and treatment was reduced to prednisolone phosphate 0.01% twice daily. One month later she returned with a 2-day history of a red, painful eye. Biomicroscopy revealed a 1.8-mm² stromal infiltrate with a dense plaque on the posterior corneal surface (Fig. 2). Gram staining of corneal scrapings revealed large numbers of Gram-negative diplococci. Treatment was begun with subconjunctival gentamicin 20 mg and topical gentamicin 15 mg/ml, hourly. Cultures subsequently grew a pure heavy growth of *Branhamella catarrhalis* from the cornea. A few colonies were isolated from the conjunctiva, and lid cultures showed a heavy mixed growth of *B. catarrhalis*, *Staphylococcus epidermidis*, and *Corynebacteria*. Antibiotic sensitivity testing showed the *B. catarrhalis* to be sensitive to gentamicin, tetracycline, chloramphenicol, neomycin, soframycin, erythromycin, and trimethoprim-sulfamethoxazole. The organism was beta-lactamase-positive and showed resistance to penicillin G and ampicillin. The inflammatory plaque on the cornea resolved, and the stromal infiltrate became less dense with only

minimal residual corneal scarring. Vision remained at counting fingers because of corneal oedema and cataract.

Discussion

Branhamella catarrhalis is a Gram-negative aerobic diplococcus belonging to the family Neisseriaceae. Formerly known as *Micrococcus catarrhalis* and *Neisseria catarrhalis*, this organism was transferred to the new genus of *Branhamella* on the basis of its cellular composition and serological cross-reactions,^{5,6} though it has also been suggested that it be included with the *Moraxella*.⁷

The Neisseriaceae include *Neisseria*, *Branhamella*, *Moraxella*, and *Acinetobacter*, of which the first 3 are obligate parasites of the mucous membranes of warm-blooded animals. With the exception of *N. gonorrhoeae* and *N. meningitidis* they are usually opportunists with low pathogenic potential. The virulence of the pathogenic *Neisseria* as opposed to other *Neisseria* and *Branhamella* may be due to the presence of a lipopolysaccharide and an IgA protease,⁸ neither of which is present in complete form in *B. catarrhalis*.^{9,10}

While *B. catarrhalis* is an unusual pathogen which tends to occur principally in immunocompromised individuals, it can be recovered from up to 9% of cases of otitis media in children¹¹ and 14% of pneumonias in patients with chronic bronchitis.¹² In addition the organism has been found in occasional cases of meningitis,¹³ endocarditis,¹⁴ and urethritis.¹⁵

Ocular infections due to *B. catarrhalis* include conjunctivitis,¹⁶ dacryocystitis,¹⁷ and endophthalmitis.¹⁸ The 3 cases of suppurative keratitis which we describe are the first in which corneal ulceration has been reported. The presence of Gram-negative diplococci in the smears of corneal scrapings of cases 1 and 3 and its isolation on culture media from all 3 cases suggest that *B. catarrhalis* was the responsible organism. The negative microscopical results from case 2 were probably due to sampling error. Caution must be exercised in the interpretation of smears, since *Moraxella* and *Acinetobacter* can be morphologically indistinguishable from *Neisseria* and *Branhamella*.

While there was no distinguishing clinical feature, each patient presented with a small localised stromal infiltrate or abscess in an area of previous corneal scarring which apparently predisposed to the secondary infection: 2 cases followed penetrating keratoplasty and the other occurred in association with vernal keratoconjunctivitis. The previous episodes of herpetic keratitis in 2 of the patients and the use of a topical corticosteroid in each case

may have additionally altered the local immunological defence mechanisms.

B. catarrhalis is generally susceptible to most antibiotics.¹⁹ The penicillins, including ampicillin, penicillin G, and penicillin V, are the most effective²⁰ followed by gentamicin, erythromycin, tetracycline, chloramphenicol, and neomycin. It is relatively resistant to vancomycin and clindamycin.¹⁴ However, recent reports have suggested an increasing occurrence of beta-lactamase production by the organism,²¹⁻²³ as we found in case 3. Since the cases of suppurative keratitis reported here showed improvement after therapy with penicillin G and gentamicin, these antibiotics should be considered for the initial therapy when the microscopical examination of corneal scrapings reveals Gram-negative cocci.

To identify accurately the causative agent of suppurative keratitis and to determine its antibiotic sensitivity, initial smears and cultures of corneal scrapings should be done whenever microbial keratitis is suspected. An organism which is normally considered to have very low pathogenicity such as *B. catarrhalis* can be capable of acting as an opportunistic pathogen in an immunologically compromised or structurally altered cornea.

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Experimental occlusion of the central artery of the retina.* I. Ophthalmoscopic and fluorescein fundus angiographic studies

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SUMMARY Transient experimental occlusion of the central artery of the retina (OCAR), lasting from 15 to 270 minutes, was produced by clamping the artery in the orbit in 63 eyes of rhesus monkeys. Ophthalmoscopic and fluorescein angiographic studies were performed before and during clamping of the artery, as well as periodically after unclamping, for periods of up to 22 weeks. The effects of transient retinal ischaemia on the retina, optic disc, and retinal vascular bed were studied. 89% of the eyes showed a variable amount of residual retinal circulation on angiography during CAR clamping, but this did not exercise any protective action against ischaemic damage. Duration of the ischaemia was the principal factor determining severity of damage. OCAR for up to 98 minutes produced no significant permanent neural damage, but OCAR for 105 minutes or longer produced irreversible permanent neural damage. There was no significant permanent damage to the retinal vascular bed, though a transient fluorescein leakage was seen after OCAR for $2\frac{1}{2}$ -3 hours or longer. The findings revealed that the normal red colour of the optic disc represents retinal vascular filling in the surface layer of the disc and not deeper vascular filling. The various factors influencing the retinal circulation and neural damage in OCAR are discussed.

Von Graefe¹ in 1859 was the first to diagnose occlusion of the central artery of the retina (OCAR) ophthalmoscopically, and he wrote a classical description of the appearance of the fundus which is still well worth reading. In spite of the tremendous amount written about OCAR since then the essential question of how long it takes for the retinal ischaemia to produce irreversible damage remains unanswered; so do many other related questions. The subject has been investigated experimentally in the rat, cat, rabbit, squirrel, monkey, and man.²⁻¹¹ These studies gave conflicting results. Moreover, the methods of producing retinal ischaemia in no way duplicated clinical OCAR in man. For example, raising the intraocular pressure to supra-arterial blood pressure^{3-7, 9, 10} not only stops the retinal circulation but also stops the choroidal circulation, which almost never occurs in clinical OCAR. In all

the previous studies the retinal integrity was evaluated either by electroretinography (ERG) or by histology, or in a few cases by both these techniques. In none of the studies was there a systematic evaluation of the retinal circulation by fluorescein fundus angiography or by fundus ophthalmoscopy during OCAR or serially thereafter during the follow-up period. It is well known that ERG, while a good indicator of the functional integrity of the photoreceptors and bipolar cells, does not give us any information about the functional status of the ganglion cells or most of the inner part of the retina, which is essentially the area involved in OCAR in man. Since it is vital for the management of this visually crippling condition to have exact information about the time that it takes for retinal ischaemia to produce irreversible damage, the present studies in rhesus monkeys were designed to find an answer to this important problem, using techniques which should duplicate as nearly as possible the natural occurrence of embolism in the CAR in man. In addition we wished to get more information on the transient acute retinal ischaemia caused by temporary OCAR, by ophthalmoscopic, angiographic, electrophysiological, and morpho-

*A brief summary of this paper formed a part of the paper presented at the American Academy of Ophthalmology meeting on 7 November 1979 at San Francisco.

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Table 1 Duration of retinal ischaemia and follow-up

Duration of retinal ischaemia (minutes)	Total no. of eyes	Duration of follow-up		
		Eyes with acute experiments	Chronic experiments	
			No. of eyes	Duration (weeks)
15-16	4	3 (Nos. 1-3)	1 (No. 4)	13½
20	2	1 (No. 5)	1 (No. 6)	14
30	1	1 (No. 7)	—	—
45	6	3 (Nos. 8-10)	3 (Nos. 11-13)	10, 13, 21
52	2	—	2 (Nos. 14-15)	20, 20
60	6	2 (Nos. 16-17)	4 (Nos. 18-21)	2*, 12, 14, 22
75	7	2 (Nos. 22-23)	5 (Nos. 24-28)	½*, 4*, 20, 20, 22
90	6	3 (Nos. 29-31)	3 (Nos. 32-34)	12, 13, 14
97	8	4 (Nos. 35-38)	4 (Nos. 39-42)	17, 17, 19, 19
102	4	4 (Nos. 43-46)	—	—
105	6	2 (Nos. 47-48)	4 (Nos. 49-52)	13, 14, 14, 16
135	6	3 (Nos. 53-55)	3 (Nos. 56-58)	13, 14, 14
270-280	5	2 (Nos. 59-60)	3 (Nos. 61-63)	3*, 13, 14
Total no. of eyes	63	30	33	

*The 4 animals died unexpectedly.

Numbers in parentheses denote the serial numbers of eyes in this study.

logical studies. This paper deals with the ophthalmoscopic and fluorescein angiographic aspects of the study. The electrophysiological and morphological studies are presented in subsequent papers.^{12 13}

Materials and methods

This study was carried out in 63 eyes of rhesus monkeys. All the eyes had stereoscopic colour fundus photography and fluorescein fundus angiography, and electroretinography (ERG) and visual evoked response (VER) recorded in their normal state.

Lateral orbitotomy was performed under general anaesthesia, with intravenous Nembutal (pentobarbitone sodium), and complete surgical asepsis. Under an operating microscope the central artery of the retina (CAR) was exposed and isolated from the attached central retinal vein and sheath of the optic nerve near its entry into the optic nerve. A microclamp was applied to the CAR. No other ocular vessel (central retinal vein or anterior or posterior ciliary arteries) was interfered with, so that the rest of the ocular circulation was normal. The wound was temporarily closed. ERG and VER were recorded within a few minutes after applying the clamp. Then fluorescein fundus angiography was performed, and in a number of eyes, colour fundus photography was done at variable intervals after clamping the CAR.

After the desired length of CAR occlusion (OCAR) (Table 1) the orbitotomy wound was opened and the clamp removed. The moment the

clamp was removed recording of ERG and VER was started, and this was usually carried on till there was recovery in the various electrophysiological functions or no further improvement was expected. The wound was stitched in layers; then colour fundus photography and fluorescein fundus angiography were repeated. In some eyes, however, the photography and angiography were performed earlier to get some information about the pattern of resolution of the fundus changes following restoration of the CAR circulation. A few hours thereafter 30 eyes were enucleated for histopathological studies. The remaining 33 eyes were followed up, mostly for about 12-22 weeks (Table 1) by serial stereoscopic colour fundus photography and fluorescein angiography, and recording of ERG and VER. After this period the eyes were enucleated either before or after the animal was perfused with a fixative solution via the heart. The eyes were examined by light microscopy and some by electron microscopy. Electrophysiological and morphological findings are reported in our subsequent papers.^{12 13}

Results

TERMINOLOGY

Before describing the results it is essential to clarify certain terms used in the description.

Posterior retina. This includes the part of the retina lying between the superior and inferior temporal retinal vessels and nasal peripapillary retina. The ophthalmoscopically apparent changes in OCAR were mostly limited to this region. Also,

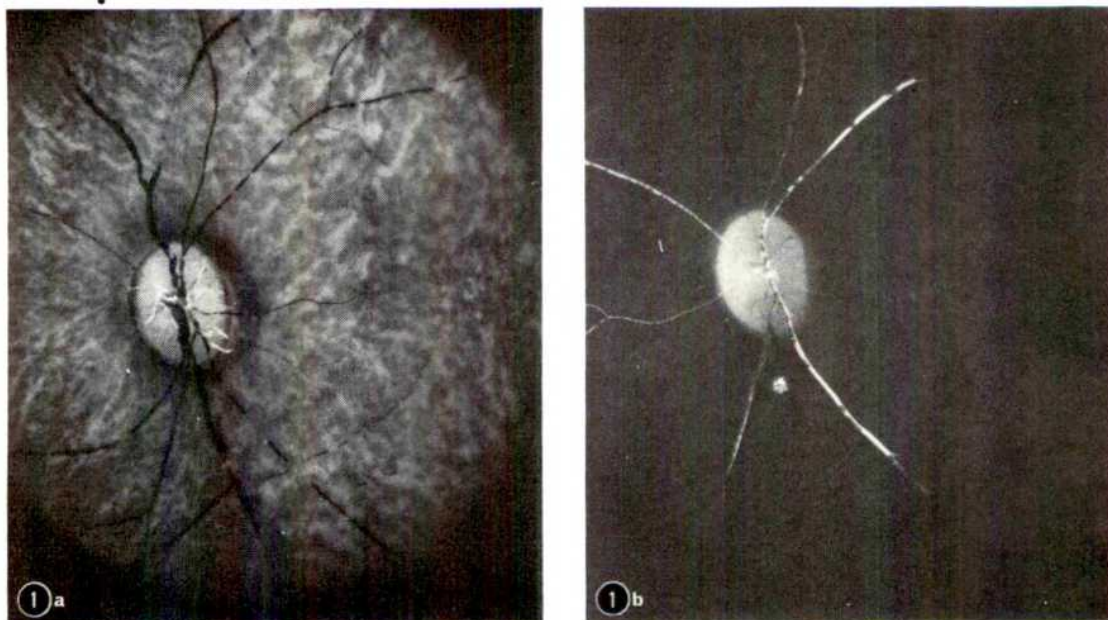


Fig. 1 Fluorescein angiograms of left eye (No. 60) 36 minutes after clamping CAR: (a) 19 seconds after injection of dye shows normal filling of disc and choroid but not of the retinal vessels which show cattle-trucking of blood column; (b) 408 seconds after the injection partial filling of main retinal arterioles seen posteriorly.

on fluorescein fundus angiography only this part of the retina could be examined satisfactorily.

Macular region. This consists of an area with a diameter of 5.25 mm, with the centre at the foveola.

Fovea. This is the central part of the macular region and is about the size of an optic disc.

Foveola. This is the central tiny spot, with avascular zone. It showed a punched-out dark brown or yellowish-brown appearance when the macular region became opaque due to ischaemia.

Retinal opacity. The ophthalmoscopic appearance of the retina soon after acute ischaemia has been described by different names, e.g., retinal oedema, milkiess, cloudiness, or opacity. We prefer the term 'retinal opacity', as appropriate to describe ophthalmoscopic findings, although light and electron microscopy may show oedema as one of the changes.

On ophthalmoscopy and fluorescein fundus angiography all eyes were perfectly normal before occlusion of the CAR.

OCULAR CIRCULATION

1. During CAR clamping. Fluorescein angiography was performed in all the eyes 5–9 minutes after the clamping.

Choroidal circulation. In all the eyes the choroidal vascular bed filled normally, demonstrating that

the posterior ciliary artery (PCA) circulation was intact and normal (Figs. 1a, 2a).

Optic disc circulation. Since the major blood supply to the disc is derived from the PCA circulation the disc showed a normal vascular filling of PCA origin (Figs. 1a, 2a).

Retinal circulation. The detailed findings from each eye are given in Table 2. A summary of the results follows.

(a) The cilioretinal arterioles. Six eyes showed the presence of cilioretinal arterioles extending temporally from the optic disc for $\frac{1}{4}$, $\frac{1}{3}$, $\frac{1}{2}$, $\frac{2}{3}$, and $\frac{3}{4}$ of the distance to the fovea, with 1 eye having the upper $\frac{1}{3}$ of the retina supplied by the cilioretinal arteriole (Fig. 2).

(b) The retinal arterioles. These started to fill from the optic disc in all except 7 eyes (Fig. 1), starting anywhere from <4 to >120 (38 ± 56) seconds after the injection of intravenous fluorescein (Table 2). In 42 eyes the arterioles filled completely in the posterior retina (Fig. 2b), taking from 3 to 275 (81 ± 65) seconds. In 14 eyes where the arterioles started to fill 14–100 (58 ± 32) seconds after the injection, they showed a partial filling for only $\frac{1}{2}$ – $\frac{2}{3}$ disc diameters' distance from the disc margin in 65–376 (164 ± 82) seconds (Fig. 1b). There was no definite relationship between the time it took for the retinal arterioles to start filling (after the

Table 2 Fluorescein fundus angiographic findings during CAR clamping

Animal number	Duration of ischaemia (minutes)	Main retinal arteriolar filling (seconds)			Capillary filling at posterior pole of retina	Miscellaneous
		Start	Complete	Partial		
2	5	20	110	—	None	None
3	6	20	—	150	None	V filling from disc in 180 s
7	6	8	<19	—	F filling in 107 s	V filling from disc
1	7	None	None	None	None	—
8	8	20	60	—	F filling in 60 s	CRA fills up to nasal margin of F
6	9	20	75	—	At 178 s fill except in F	—
9	9	33	150	—	None	—
12	10	None	None	None	None	—
61	10	100	—	250	None	—
20	11	20	70	—	None	—
10	11	23	150	—	D-F fill at 150 s	CRA fills up to 1/3 of D-F V fill at 150 s
4	12	43	—	120	None	—
56	12	20	150	—	None	—
5	13	Gradual	70	—	In PP only	—
55	14	20	62	—	None	—
57	15	50	200	—	None	V fill from optic disc
24	16	15	130	—	None	—
40	17	None	None	None	None	—
54	17	12	50	None	None	Nasal retina filled well
62	17	20	110	—	None	—
21	18	10	26	—	Post pole fill at 60 s	—
52	18	17	24	—	Mac fill at 70 s	Normal retinal vascular bed filling at 180 s
58	18	20	26	—	Post pole fill at 50 s	—
14	19	6	14	—	Some perimac fill by 196 s	—
13	20	12	27	—	None	—
41	20	50	—	132	None	—
47	20	100	—	260	None	—
48	20	7	14	—	Post pole fill	CRA fills up to 1/3 retinal vascular bed
26	20	31	125	—	None	CRA fills up to 1/4 D-F
42	21	6	20	—	Post pole fill by 75 s	CAR fills slowly with complete V fill in 75 s
18	22	20	200	—	None	—
39	23	30	250	—	Some fill in PP	—
59	23	None	None	None	None	—
53	24	20	85	—	Up to centre of F by 5 min	—
16	25	None	None	None	None	—
17	25	14-37	128	—	In PP up to 2/3 D-F	—
27	25	21	120	—	None	—
19	26	20	—	191	None	—
50	26	14-33	300	—	None	Main and branch A fill
25	26	40	—	250	None	—
15	27	36	72	—	In PP up to F margin by 100 s	—
28	27	None	None	None	None	—
63	28	20	180	—	None	—
32	31	38	—	120	None	—
29	33	100	—	300	None	—
30	35	20	?	—	None	Cattle-trucking in A. Small vessels fill in mac
34	35	>26	<154	—	In mac except F fill at 154 s	—
31	35	20	140	—	None	—
49	35	30	200	—	None	—
60	36	60	—	436	None	Cattle-trucking in A
51	38	14	—	185	None	CRA fills up to 1/2 D-F
33	41	Very slow	?	—	None	—
22	45	100	—	350	None	—
23	45	30	100	—	None	—
36	70	12	26	—	PP fill by 200 s	CRA fills up to 2/3 D-F
38	71	20	140	—	None	—
37	75	40	150	—	None	—
35	81	60	—	230	None	—
44	85	None	None	None	None	—
43	90	30	130	—	None	—
45	90	<4	6	—	Post pole except central F at 10 s and F at 20 s	V fill completely at 60 s
46	90	10	20	—	None	—
11	? <30	60	—	125	None	—

A = Retinal arterioles, V = Retinal veins, CRA = Cilioretinal artery, Post = Posterior, PP = Peripapillary region, S = Seconds, D-F = Disc to foveolar region, F = Foveal region, Mac = Macular region.
All the time for filling of vessels from intravenous injection of fluorescein.

intravenous injection of fluorescein) and the time that elapsed before the complete/partial filling was finished.

(c) *The retinal capillary bed at the posterior pole.* This filled completely in 9 eyes (in 16–280 (80 ± 85) seconds) (Fig. 3) and partially in 9 more eyes (in 64–220 (147 ± 52) seconds). There were cilioretinal

arterioles in 2 of the former and 2 of the latter group, while in the other 2 eyes with cilioretinal arterioles there was no appreciable filling of the retinal capillaries (Fig. 2). In the remaining eyes the fluorescein usually filled only the main retinal arterioles without any extension to their smaller branches.

(d) *The retinal veins.* There was no retinal venous

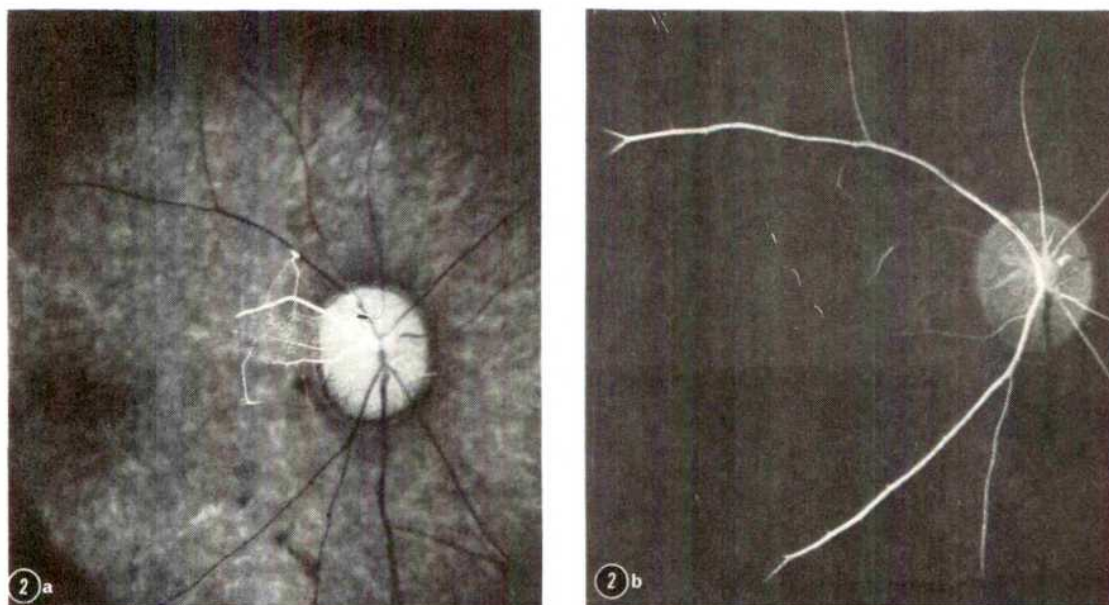
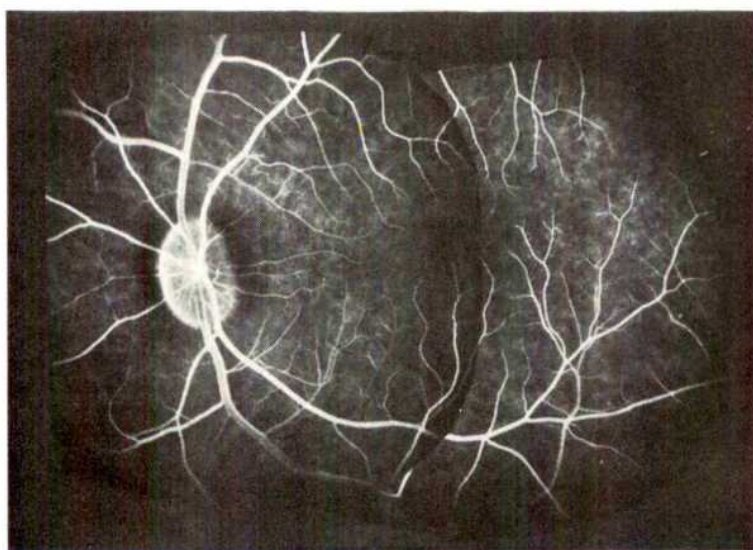


Fig. 2 Fluorescein angiograms of right eye (No. 26) 25 minutes after clamping CAR: (a) 7 seconds after injection of dye shows normal filling of choroid, disc and a cilioretinal artery but empty retinal vessels; (b) 125 seconds after the injection shows filling of the main retinal arterioles only.

Fig. 3 Composite fluorescein angiogram of left eye (No. 8) 8 minutes after clamping CAR showing complete filling of the retinal vascular bed 206 seconds after injection of dye.



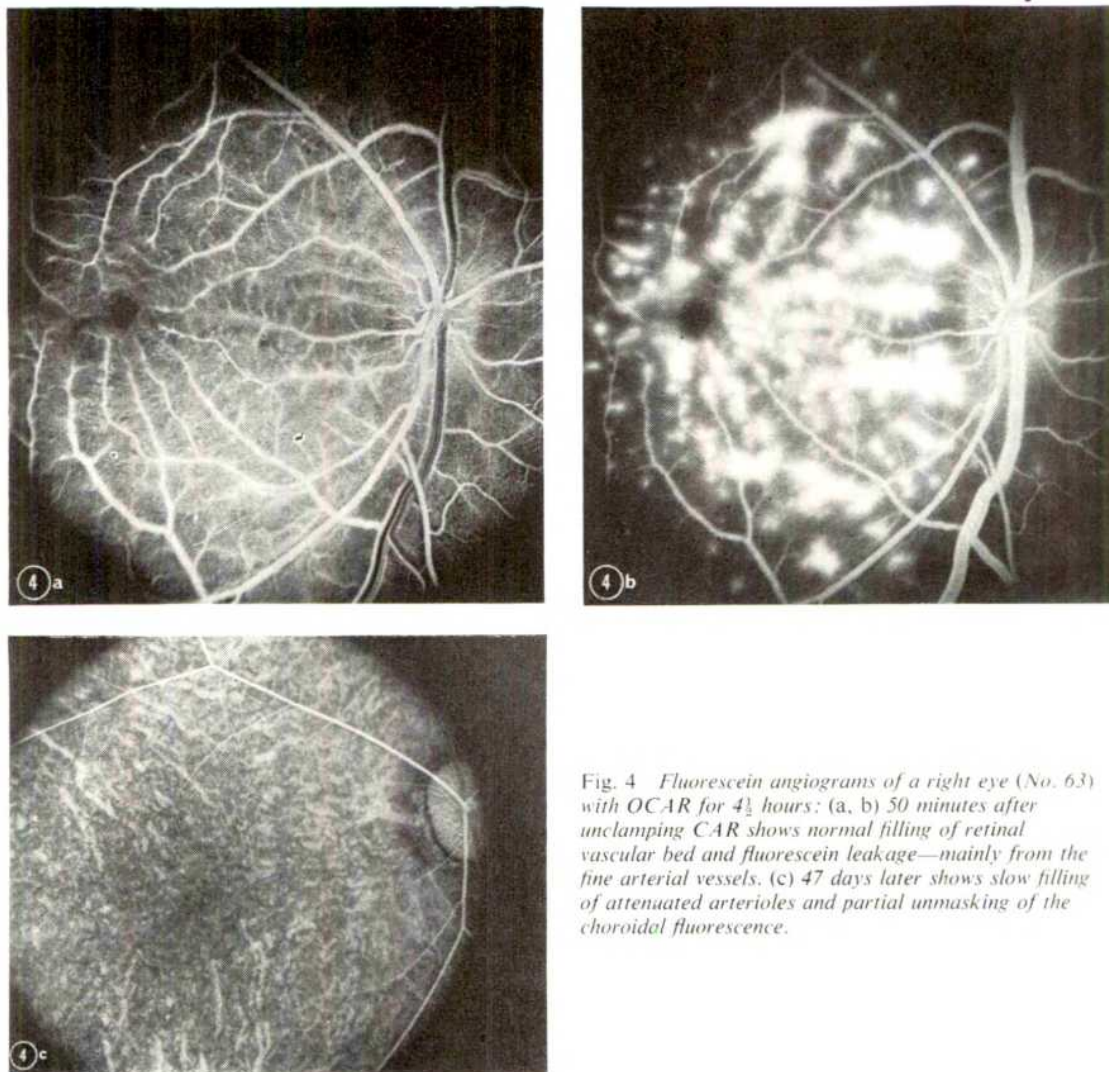


Fig. 4 Fluorescein angiograms of a right eye (No. 63) with OCAR for 4½ hours: (a, b) 50 minutes after unclamping CAR shows normal filling of retinal vascular bed and fluorescein leakage—mainly from the fine arterial vessels. (c) 47 days later shows slow filling of attenuated arterioles and partial unmasking of the choroidal fluorescence.

filling except in 6 eyes. In 3 of these (Nos. 10, 42, 45) the veins filled completely (Table 2) and in the remaining 3 eyes (Nos. 3, 7, 57) retrograde filling of the retinal veins from the optic disc was seen (most probably due to some compression of the central retinal vein in the orbit of these eyes).

II. *After unclamping CAR.* The retinal circulation was evaluated in all eyes immediately after unclamping the CAR. The time intervals between removing the clamp and the angiography varied in different eyes, but it was usually about 5 minutes after taking the colour fundus photographs (Table 4 below).

In all the eyes the retinal circulation was restored to its normal preclamping state with normal

filling of the retinal arterioles, capillaries, and veins (Figs. 4a, 5a). No abnormality of any kind was detected in eyes with OCAR up to 105 minutes. Two eyes (Nos. 56, 58) with ischaemia for 2½ hours showed a very mild fluorescein leak from the capillaries at the tips of some of the macular vessels, with no other abnormality. In eyes with OCAR for 4½ hours angiography ¾–1¾ hours after unclamping the CAR showed marked fluorescein leakage from the macular vessels in all eyes, being mostly along the retinal venules in 2 eyes (Nos. 59, 62) arterioles in 2 (Nos. 60, 63), and both venules and arterioles in one (No. 61) (Figs. 4, 5).

On follow-up, in all but 2 eyes with retinal ischaemia up to 97–98 minutes, the retinal circulation

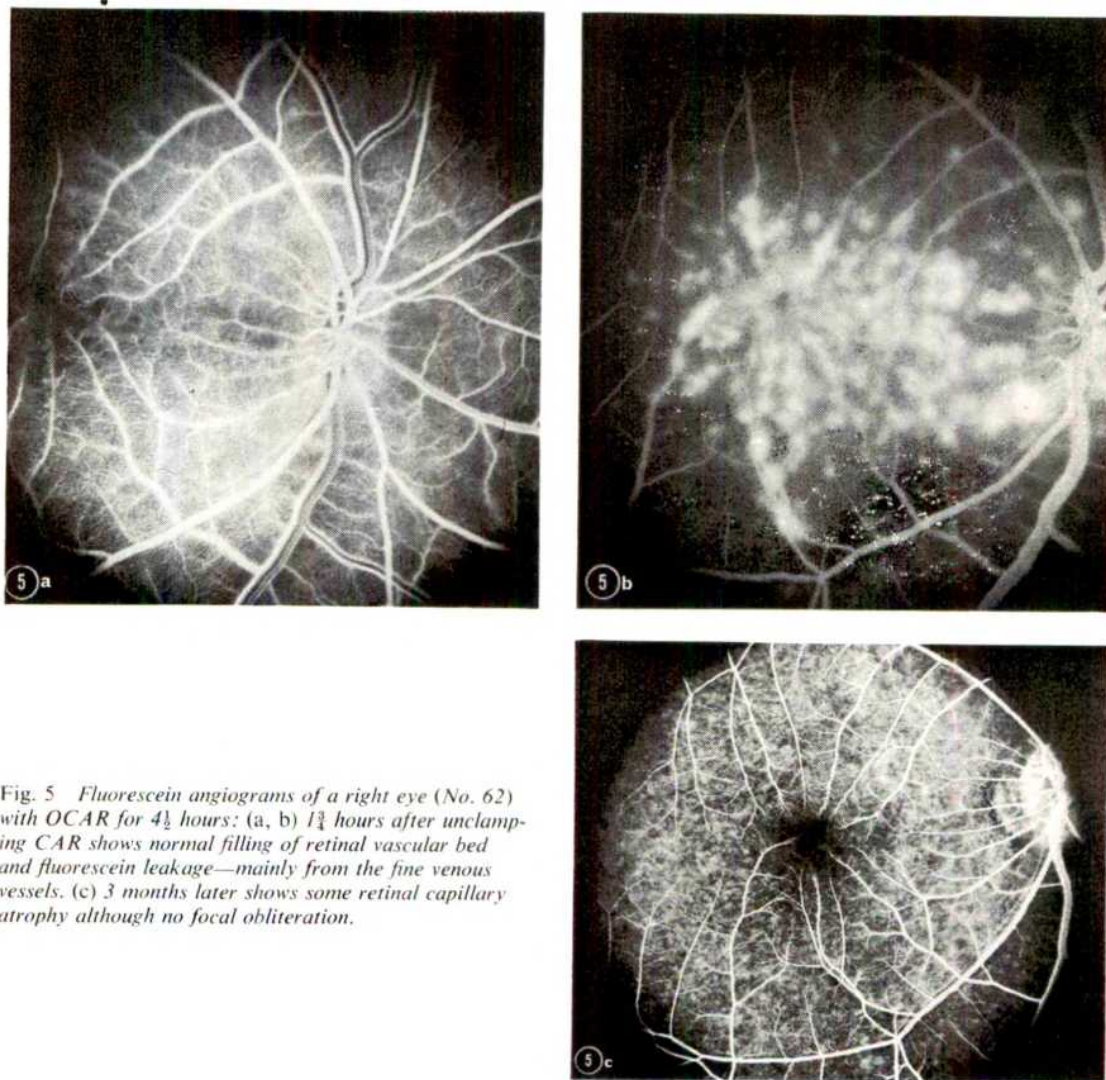


Fig. 5 Fluorescein angiograms of a right eye (No. 62) with OCAR for 4½ hours: (a, b) 1¼ hours after unclamping CAR shows normal filling of retinal vascular bed and fluorescein leakage—mainly from the fine venous vessels. (c) 3 months later shows some retinal capillary atrophy although no focal obliteration.

remained perfectly normal throughout with retinal capillaries normally outlined; there was no other angiographic abnormality. In 2 eyes with 75 minutes' ischaemia, however, the retinal capillaries were poorly defined, and their overall population was reduced.

In eyes with retinal ischaemia of 105 minutes or longer the retinal capillaries and retinal pigment epithelium showed abnormalities. In the 2 eyes with OCAR for 2¼ hours (Nos. 56, 58) and fluorescein leakage soon after unclamping the artery the leak disappeared the next day. In eyes with retinal ischaemia of 4½ hours' duration the fluorescein leakage seen in the macular region (see above) was either less or had almost vanished on the day

following unclamping; it disappeared in all cases in 4–5 days, leaving normal filling of the retinal capillaries. In all eyes with retinal ischaemia of 105 minutes or more the retinal capillaries were normally outlined during the initial follow-up of 2–3 weeks, but after this period the capillaries were progressively less well outlined, though no localised capillary closure was seen in any eye. With longer follow-up it seemed that there was an overall narrowing of the capillary lumen, and their population was somewhat reduced (Fig. 5c), and there was some delay in filling of the CAR (Fig. 4c).

OPHTHALMOSCOPIC APPEARANCES

1. During CAR clamping. Table 3 gives the details

Table 3 Ophthalmoscopic findings during CAR clamping

Animal number	Duration of ischaemia (minutes)	Posterior retinal opacity	Opacity of foveal retina	Brown spot	Retinal vessels	Optic disc
40	7	Mild	Slight	None	Full, mild cyanosis	Pale
24	13	Mild	Mild	—	Full, slight narrowing	Pale
13	15	Moderate	Mild	—	Normal-looking	Normal
26	15	Moderate	Moderate	—	Full and narrow	Pale
41	16	Moderate	Mild	—	Full, cyanotic, narrow	Pale
15	17	Slight	Slight	None	Normal-looking	Normal
42	18	Slight	Almost normal	None	Full, normal-looking	Normal
16	19	Slight	Slight	None	Full, normal-looking	Normal
28	20–22	Marked	Marked	—	Marked narrowing. A and V cattle-trucking	Pale
27	15–20	Mild-Moderate	Mild	None	Full, slight-narrowing	Pale
25	20	Moderate	Moderate	—	Full, slight narrowing	Pale
39	20	Mild	Slight	None	Full, normal-looking	Mild pallor
14	24	Marked	Marked	—	Full, normal-looking	Pale
31	25	Marked	Marked	—	A and V cattle-trucking	Pale
23	30	Moderate	Moderate	—	Full, normal-looking	Pale
22	35	Marked	Marked and ILMW	—	Full and narrow	Pale
36	60	Marked	Severe	—	Normal-looking	Almost normal-looking
37	70–75	Severe	Severe	—	A-marked narrowing, V cattle-trucking	Pale
38	70	Marked	Severe	—	Full and narrow	Pale
43	70–75	Severe	Severe	—	Marked narrowing, V cattle-trucking	Pale
44	75	Severe	Severe and ILMW	—	Extremely narrow, A and V cattle-trucking	Pale
46	78	Severe	Severe and foveal star	—	Full, normal-looking, Markedly sheathed main A	Pale
29	78	Severe	Severe	—	A-extremely narrow, A and V cattle-trucking	Pale
35	71–77	Severe	Severe	—	As above	Pale
45	90	Moderate*	Marked*	—	A normal-looking, V engorged	Hyperaemic
58	113	Severe	Severe	—	Pariarterial sheathing	Pale

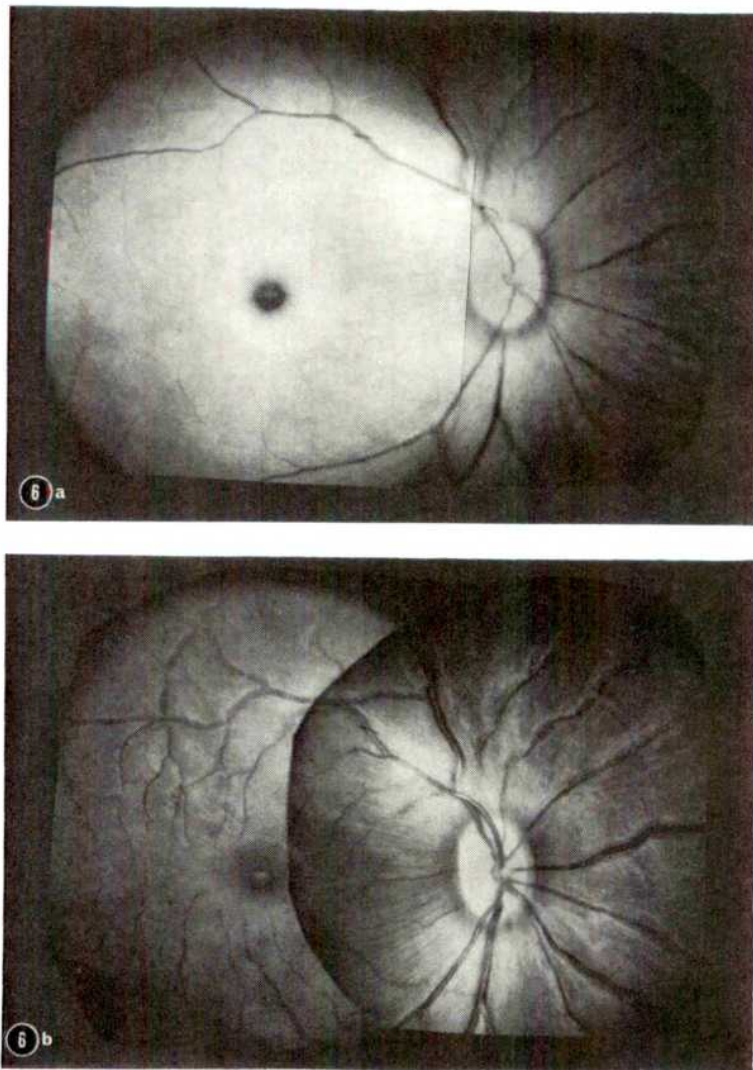
A = Retinal arterioles, ILMW = Internal limiting membrane wrinkling, V = Retinal veins.

*With Christmas tree pattern of normal-looking retina around arterioles.

of findings in 26 eyes of the present series arranged in order of duration of retinal ischaemia. When the earliest fundus examination was performed, 7 minutes after OCAR, the posterior retina already showed a mild degree of opacity with a pale disc; the retinal vessels were full of blood and mildly cyanotic. Thirteen minutes after OCAR the picture was almost similar. In 3 eyes 15–16 minutes after OCAR the retinal opacity was of moderate degree with a pale disc. However, in 3 eyes 17–19 minutes after OCAR there was only a slight retinal opacity of the posterior pole with a normal-looking optic disc. In 4 eyes about 20 minutes after OCAR the retinal opacity varied from mild to marked with a pale disc, though on angiography there were no gross differences except that the eye with marked

retinal cloudiness had no retinal circulation at all compared to some arterial filling in the rest. Twenty-four to 60 minutes after OCAR the opacity was marked in the posterior retina, with almost normal-looking peripheral retina, and the disc was pale. Seventy minutes and longer after OCAR there was a severe degree of opacity of the posterior retina, with a pale optic disc (Fig. 6a). The severity of retinal opacity increased with the increase in duration of ischaemia, and was usually greatest in the foveal zone, which in severe cases was swollen, and in some cases also showed wrinkling or other changes of the internal limiting membrane (ILM). The central foveola always showed a well-defined punched-out brown spot after an ischaemia of 20 minutes or longer with marked or severe opacity of

Fig. 6 Composite fundus photographs of a left eye (No. 38): (a) 66 minutes after clamping CAR shows retinal opacity with a well-defined brown spot at the foveola. (b) $3\frac{3}{4}$ hours after unclamping the CAR (after 97 minutes' OCAR) shows almost normal-looking fundus.



the foveal retina (Fig. 6a) and not always so distinct a brown spot with moderate opacity; the brown spot is equivalent to the classical cherry red spot in OCAR in Caucasians. The retinal vessels showed narrowing (more marked in the arteries than in the veins) which was most marked with severe retinal opacity, so much so that in the latter group the arteries were reduced to extremely thin lines. The longer the ischaemia, the narrower the vessels became, most probably due to retinal oedema compressing the vessels. In eyes with severe opacity there was usually segmentation of the blood column ('cattle-trucking') in both arteries and veins—more often in the latter than the former. However some eyes showed the cattle-trucking with less marked

opacity as well (Fig. 1). Periarterial sheathing of the main retinal arteries was seen in 2 eyes (Nos. 46 and 58). In some eyes the retinal vessels appeared almost normal in spite of mild to marked retinal opacity (Nos. 13–16, 23–36, 39, 42, 45).

II. After unclamping CAR.

(A) Within a few hours after unclamping the CAR. Detailed findings in the various eyes are shown in Table 4. The fundus appeared normal when seen $\frac{1}{2}$ –1 hour after restoration of circulation in eyes with retinal ischaemia of up to 20 minutes. In an eye with ischaemia for 30 minutes the fundus was normal when seen $1\frac{3}{4}$ hours after unclamping the CAR. Ischaemic changes following 45–52 minutes of OCAR had disappeared $2\frac{1}{4}$ – $3\frac{1}{4}$ hours later,

Table 4 Ophthalmoscopic findings soon after unclamping CAR

Animal number	Duration of ischaemia (minutes)	Time since CAR unclamping (minutes)	Retina	Foveal region	Brown spot	Retinal vessels	Optic disc
1	15	60	Normal	Normal	None	Normal	Normal
2	15	30	Normal	Normal	None	Normal	Normal
3	15	40	Normal	Normal	None	Normal	Normal
4	16½	26	Normal	Normal	None	Normal	Normal
6	20	60	Normal	Normal	None	Normal	Normal
7	30	105	Normal	Normal	None	Normal	Normal
11	45	1 day	Normal	Normal	None	Normal	Normal
8	45	10	Opacity in PP and post pole	Opaque	None	Normal	? Pale
12	45½	1 day	Normal	Normal	None	Normal	Normal
13	45	195	Almost normal	Normal	None	Normal	Normal
10	45	135	Normal	Normal	None	Normal	Normal
14	52	68	Slight opacity ST and IT to disc	Mild opacity	None	Normal	Normal
15	53	195	Normal	Normal	None	Normal	Normal
20	60	60	Mild opacity post pole	Yellowish	None	Normal	Normal
16	60	135	As above	Mild opacity	None	Normal	Normal
18	60	144	As above	Mild opacity	None	Normal	Normal
21	60	113	Mod opacity post pole	Mod opacity	?	Normal	Normal
19	60	101	As above	Mod opacity	?	Normal	Normal
17	60	130	As above	Mod opacity	?	Normal	Normal
26	75	135	As above	Mod opacity	?	Normal	Normal
22	75	180	Faint opacity ST and IT to disc	Mild opacity and ILM folds	?	Normal	Normal
28	75	165	As above	Very mild opacity	?	Normal	Normal
27	75	165	Opacity mainly along arc fib*	Mild opacity	?	Normal	Normal
23	75	240	Normal-looking	Normal-looking	None	Normal	Normal
25	75	180	Normal-looking	Normal-looking	None	Normal	Normal
24	74	180	Normal-looking	Normal-looking	None	Normal	Normal
32	90	16	Mild opacity	Mild opacity	None	Normal	Normal
29	90	180	Almost normal	Almost normal	None	Normal	Normal
33	90	180	Almost normal	Almost normal	?	Normal	Normal
30	90	180	Almost normal	Slight opacity	None	Normal	Normal
34	90	100	Some opacity	Slight opacity	None	Normal	Normal
31	90	135	Some opacity	Slight opacity	Yellow spot	Normal	Normal
35	97	270	Almost normal	Almost normal	None	Normal	Normal
36	97	270	Almost normal	Almost normal	None	Normal	Normal
37	97	270	Faint opacity	Almost normal	None	Normal	Hyperaemic
38	97	225	Normal-looking	Mild opacity	None	Normal	Normal
41	97	150	Mild opacity	Mild opacity	None	Normal	Normal
39	98	150	Mild opacity	Normal	None	Normal	Normal
42	97	150	Almost normal	Mild opacity and ILMW	None	Normal	Normal
40	97	150	Slight opacity	Slight opacity	None	Normal	Normal
43	102	285	Mild opacity	Mild opacity	None	Normal	Normal
44	102	270	Mild opacity	Mild opacity with ILMW	None	Normal	Normal
45	102	225	Mild opacity	Mild opacity	None	Normal	Normal
46	102	300	Mild opacity	Mild opacity	Present	Normal	Slightly blurred margins
52	105	138	Slight opacity	Slight opacity with ILMW	None	Normal	Normal
50	105	150	Slight opacity	Mild opacity	?	Normal	Normal
49	105	210	Mild-moderate opacity	Mild-moderate opacity	Present	Normal	Slightly hyperaemic
47	105	60	As above	As above	Present	Normal	Hyperaemic
51	105	210	Mod opacity	Mod opacity	Present	Normal	Hyperaemic
48	105	105	Mod opacity**	Mod opacity	Present	Normal	Normal
58	138	1 day	Marked opacity	Marked opacity with ILMW	Present	Normal	Hyperaemic
56	134	23	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
54	135	150	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
57	135	30	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
55	146	135	Marked opacity	Marked opacity	Present	Normal	Hyperaemic
61	275	1 day	Marked opacity	Marked opacity with ILMW	Present	Normal	?
62	280	90	Marked opacity	Marked opacity and oedema with ILMW	—	Periart sheathing	Hyperaemic
59	270	68	Marked opacity	As above	—	—	Hyperaemic
63	270	45	Marked opacity	As above	Present	—	Normal
60	270	60	Marked opacity	Marked opacity and oedema	Present	—	Hyperaemic

ILM = Internal limiting membrane. ILMW = ILM wrinkling. Mod = Moderate. Post = Posterior. PP = Peripapillary region. IT = Inferior temporal. ST = Superior temporal. Arc fib = Arcuate fibers. Periart = Periarterial.

*Peripapillary retina normal. **Upper half of retina normal because of big cilioretinal artery.

except for some prominent white nerve fibre striation near the superior temporal and inferior temporal margin of the disc in some eyes. In eyes with OCAR lasting for 1 hour the retina still showed mild to moderate retinal opacity, especially along the arcuate fibres, $1\frac{3}{4}$ – $2\frac{1}{4}$ hours after unclamping the CAR though the optic disc looked normal. Retinal changes due to 75–90 minutes' ischaemia had recovered almost to normal $4\frac{1}{2}$ hours after restoration of the circulation and the optic disc was normal. In eyes with ischaemia of 97 minutes the fundus looked almost normal $3\frac{3}{4}$ – $4\frac{1}{2}$ hours after unclamping the CAR or showed faint retinal opacity with normal optic disc (Fig. 6b) while $2\frac{1}{2}$ hours after the release of the clamp it showed variable degrees of retinal opacity. In eyes with retinal ischaemia for 102 minutes mild retinal opacity was still evident $4\frac{1}{2}$ –5 hours after restoration of circulation, though the optic disc was normal-looking by then. Eyes with retinal ischaemia of 105 minutes, when seen $3\frac{1}{2}$ hours after unclamping the CAR, still showed mild to moderate retinal opacity and a normal-looking or hyperaemic optic disc. When retinal ischaemia was of $2\frac{1}{4}$ hours' duration the retina did not show much recovery that day and the optic disc was always hyperaemic. Eyes with OCAR of $4\frac{1}{2}$ hours showed marked retinal opacity, marked at the upper and lower poles of the optic disc, and there was detachment of the ILM in the foveal zone in 3 (Nos. 59, 62, 63) of the 5 eyes with marked oedema in that region and the disc was usually hyperaemic with slightly blurred margins. When the retinal oedema was marked the macular retina showed folding in the foveal region, producing a ridge or a cruciform elevation.

In summary, on restoration of circulation after OCAR (a) in eyes with 90 minutes' ischaemia or less the retina and optic disc looked normal within $4\frac{1}{2}$ hours, (b) eyes with occlusion for 97 and 102 minutes showed a normal-looking disc, but the retina showed mild opacity in the latter group and faint opacity or a normal appearance in the former group, and (c) in eyes with OCAR for 105 minutes or longer the ischaemic fundus changes did not resolve.

(B) *During follow-up period.* Thirty-three eyes were followed up for up to 22 weeks (Table 1). The findings fall naturally into the following 3 groups.

(a) *15–90 minutes' retinal ischaemia.* In eyes with retinal ischaemia of 90 minutes or less the retina and optic disc mostly remained normal during the entire period of follow-up except for a few eyes showing some unusual changes which were as follows:

1. One eye with 45 minutes' ischaemia developed during the 2nd–3rd week transient wrinkling of the

ILM in the macular region; this lasted a few weeks, leaving a normal retina after that.

2. One eye with 52 minutes' ischaemia showed some residual retinal opacity in the foveal zone after the first day; this cleared during the first week. This eye showed a slight pallor of the optic disc after about 2 weeks.

3. Two eyes after OCAR of 75 minutes developed pallor of the optic disc in about 2 weeks; this gradually progressed to optic atrophy which was maximum by about the fifth week, by which time the retina of these 2 eyes also looked atrophic.

4. In the eyes with retinal ischaemia of 90 minutes the fundus looked perfectly normal in 1 week, but 1 eye showed some doubtful optic disc pallor.

(b) *97 minutes' retinal ischaemia.* In all the eyes the retina was normal-looking throughout the period of follow-up (Fig. 7). In about 2–3 weeks the optic disc developed a slight pallor which did not progress.

(c) *105–270 minutes' retinal ischaemia.* In all these eyes the retinal opacity and oedema worsened on the day after the unclamping of the CAR, compared to what was seen a few hours after the unclamping. The retinal changes started to resolve before the end of the first week, leaving retinal opacity mainly in the macular region and along the superior and inferior arcuate fibres, with some radial wrinkling of the ILM. The retinal opacity and wrinkling of the ILM cleared within 2, 2–3, and 3 weeks after the ischaemia in eyes with retinal ischaemia of 105, 135, and 270 minutes respectively, leaving an atrophic retina and attenuated retinal vessels. In the second or third week fine crystalline deposits developed in the retina, mainly in the macular region, in half the eyes with 105 minutes' ischaemia and in all the eyes with 135 and 270 minutes' ischaemia. These crystalline deposits cleared after variable time intervals, usually in about 2 months, but persisted in a few eyes even up to the end of follow-up (Fig. 8). The detachment of the ILM in the foveal zone, seen in 3 of 5 eyes after ischaemia of 270 minutes, cleared in 4–5 weeks.

The optic disc started to develop pallor during the first week and marked optic atrophy was seen in the second or third week, without much change thereafter.

The retinal pigment epithelium showed granularity at the posterior pole in all eyes with retinal atrophy, i.e., 105 minutes' and longer ischaemia, and 2 eyes with 75 minutes' ischaemia. This usually developed gradually 3 weeks after the OCAR. It never developed into gross pigmentary disturbance.

(C) *The final ophthalmoscopic appearance at the end of follow-up.* This is given for each eye in Table 5. In all eyes with retinal ischaemia of up to 97–98

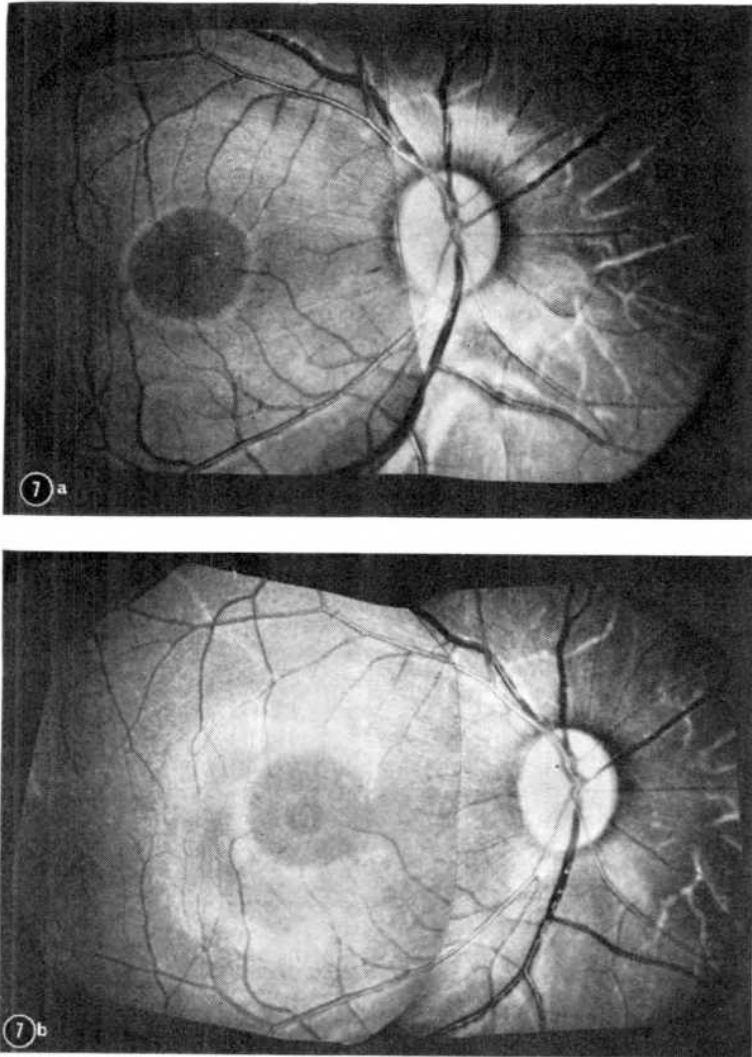


Fig. 7 Composite fundus photographs of a right eye (No. 42): (a) Normal fundus before clamping of CAR. (b) 4 months after 97 minutes' OCAR shows normal-looking fundus.

minutes (except 2 eyes with 75 minutes' ischaemia) the retina was normal-looking ophthalmoscopically (Fig. 7b). The optic disc was normal in all eyes except for a doubtful pallor of the disc in one eye with 90 minutes' ischaemia, and a slight pallor in 1, 1, and all 4 eyes with 52, 75, and 97 minutes' ischaemia respectively.

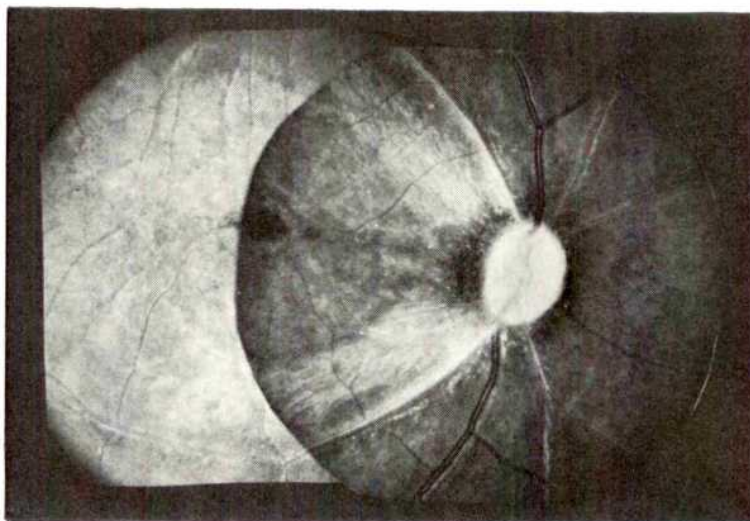
In 2 eyes with 75 minutes' ischaemia and in all eyes with ischaemia of 105 minutes or longer the retina and optic disc were markedly atrophic with attenuated retinal vessels; a few eyes showed fine crystalline deposits in the retina at the posterior pole (Fig. 8). However, 2 (Nos. 50, 52) of the 4 eyes with 105 minutes' ischaemia showed a more or less normal-looking retina; but this is an ophthalmo-

scopic artefact and deceptive, because the optic disc was markedly atrophic.

INFLUENCE OF RESIDUAL RETINAL CIRCULATION ON RETINAL RECOVERY/SURVIVAL TIME

This is an extremely important consideration and was especially investigated in the present study. Table 2 summarises the fluorescein angiographic findings on residual retinal circulation in each eye. Tables 4 and 5 summarise the ophthalmoscopic findings in each eye soon after unclamping the CAR and at the end of follow-up, respectively. A comparison of Table 2 with Table 4 or 5 revealed no well-defined correlation. Consider, for example, the

Fig. 8 Composite fundus photographs of right eye (No. 62): 7 weeks after $4\frac{1}{2}$ hours' OCAR showing complete atrophy of the disc and retina, sheathing of main retinal arterioles, crystalline retinal deposits, and foveal degeneration. Angiograms of this eye soon after unclamping CAR are shown in Fig. 5.



various eyes of the 75- and 105-minute groups.

This lack of correlation was found almost throughout the series, so that neither the absence of retinal circulation, nor the filling of the main retinal arterioles (complete or partial), nor the filling of retinal capillaries in a part or the entire posterior pole, made any significant difference to the final outcome of retinal ischaemia; nor did the presence of cilioretinal arterioles prevent damage to the part of the retina supplied by the occluded central retinal artery. In eyes with 105 minutes' OCAR or longer complete or partial filling of the retinal circulation as compared to minimal or no filling did not protect the retina from irreversible damage. This was the most unexpected finding of this study and contradicts all the previous assumptions.

Discussion

RESTORATION OF RETINAL CIRCULATION AFTER OCAR

For well over a century, in eyes with OCAR, filling of the retinal arteries on ophthalmoscopy has been described when the patient is first seen within a few days or sometimes even within a few hours after the onset of loss of vision. This has led to considerable controversy, not only about the mechanism responsible but also about the basic nature of the lesion causing OCAR. The residual retinal circulation after OCAR and its subsequent improvement have been thought to be due to (1) cilioretinal anastomoses in the optic nerve head,¹⁴⁻¹⁶ (2) the transient nature of systemic arterial hypotension in eyes with stenosed CAR producing OCAR,^{15 17}

(3) transient spasm of the CAR,¹⁸ (4) dislodging of an embolus in CAR¹⁹ or ophthalmic artery,²⁰⁻²² (5) incomplete OCAR,²³ and (6) retrograde flow from the anterior ciliary arteries.² The last possibility evidently is illogical while the others remain probabilities (except for the dislodging of an ophthalmic artery embolus).

In the present study occlusion of the CAR near its entry into the sheath of the optic nerve by the clamp was complete and indubitable, and yet fluorescein angiography performed immediately after clamping the artery revealed a variable amount of residual retinal circulation in 89% of the eyes. Hill,²⁴ in 10 patients with OCAR seen $\frac{1}{2}$ -4 days after the onset of occlusion, found on fluorescein angiography normal retinal circulation in 3 eyes (in $\frac{1}{2}$, 1, 4 days), slightly delayed circulation in 3 eyes (in 1, 1, 2 days), delayed in 2 (in $\frac{1}{2}$, 1 day), and no filling of the CAR in 2 eyes (in $\frac{1}{4}$, 1 $\frac{1}{2}$ day). If eyes with permanent OCAR are followed up in patients^{25 26} or in rhesus monkeys with experimental occlusion,^{27 28} a slow restoration to almost normal retinal circulation is seen in almost all eyes within a few days after the occlusion. Thus, the presence of retinal circulation on fluorescein angiography in eyes seen a few hours or days after OCAR is no proof of nonoccurrence or incompleteness of the occlusion.

It appears that the residual retinal circulation or its restoration in OCAR is most probably due to the following 2 anastomoses.

(1) *Cilioretinal capillary anastomoses.* The optic disc is supplied essentially by the posterior ciliary arterial (PCA) circulation in the lamina cribrosa and prelaminar regions (Figs. 1a, 2a), and by the retinal circulation in the surface layer.^{25 29} The 2

Table 5 *Ophthalmoscopic findings at the end of follow-up in chronic experiments.*

<i>Animal number</i>	<i>Duration of ischaemia (minutes)</i>	<i>Follow-up period (weeks)</i>	<i>Optic disc</i>	<i>Retina</i>	<i>Macular region</i>	<i>Retinal vessels</i>
4	16½	13½	Normal	Normal	Normal	Normal
6	20	14	Normal	Normal	Normal	Normal
11	45	10	Normal	Normal	Normal	Normal
12	45½	13	Normal	Normal	Normal	Normal
13	45	21	Normal	Normal	Normal	Normal
14	52	20	Sl pallor	Normal	Normal	Normal
15	53	20	Normal	Normal	Normal	Normal
20	60	14	Normal	Normal	Normal	Normal
18	60	2*	Normal	Normal	Normal	Normal
21	60	22	Normal	Normal	Normal	Normal
19	60	12	Normal	Normal	Normal	Normal
26	75	20	Atrophic	Atrophic	ILM reflex	Normal
28	75	22	Sl pallor	Normal	Normal	Normal
27	75	20	Atrophic	Atrophic	ILM reflex	Normal
25	75	4*	Normal	Normal	Normal	Normal
24	74	½*	Normal	Normal	Normal	Normal
32	90	12	? Sl pallor	Normal	Normal	Normal
33	90	13	Normal	Normal	Normal	Normal
34	90	14	Normal	Normal	Normal	Normal
41	97	19	Sl pallor	Loss of NFS except in PMB	Yellow foveal discolouration	Normal
39	98	17	Sl pallor	Normal	Normal	Normal
42	97	19	Sl pallor	Normal	Normal	Normal
40	97	17	Sl pallor	Normal	Normal	Normal
52	105	16	Atrophic	Normal-looking	Normal	Normal
50	105	14	Atrophic	Normal-looking	Normal	Normal
49	105	13	Atrophic	Atrophic	Atrophic	Narrow
51	105	14	Atrophic	Atrophic	Atrophic	Narrow
58	138	14	Atrophic	Atrophic	Atrophic	Normal-looking
56	134	13	Atrophic	Atrophic	Atrophic	Narrow
57	135	14	Atrophic	Atrophic	Atrophic	Narrow
61	275	3	Atrophic	Atrophic	Atrophic	Narrow
62	280	13	Atrophic	Atrophic	Atrophic with old ILMD border markings	Narrow
63	270	14	Atrophic	Atrophic	Atrophic with old ILMD border markings	Narrow

*Animal died during follow-up. ILMD = Internal limiting membrane detachment, ILM = Internal limiting membrane, NFS = Nerve fibre striation, PMB = Papillomacular bundle, Sl = Slight.

circulations communicate via the capillaries of the optic disc, so that, in OCAR, capillaries on the surface of the optic disc (Fig. 1a), and even in the peripapillary retina, can fill from the ciliary circulation of the disc. Soon after OCAR, these anastomoses do not seem to contribute to the filling of the CAR to any appreciable extent, but after a few weeks these enlarge sufficiently.²⁵⁻²⁸

(2) *Anastomoses by the CAR.* The artery in man gives out pial branches in 95% and a variable number of branches within the optic nerve in 75% of cases.³⁰ The pial branches in the great majority of cases establish prominent anastomoses with other pial branches arising from other sources (described and illustrated in detail elsewhere).³⁰ At the lamina cribrosa the CAR gives no branches. In the present study, with the site of OCAR outside the optic nerve, all the pial collaterals would still be present and lead to filling of the CAR beyond the site of occlusion. This was strongly suggested by the fact that the CAR started to fill from its intraneural course and that in a number of these eyes (e.g., Nos. 7, 13, 14, 21, 36, 42, 45, 46, 48, 52, 58) once the filling of the artery started the flow was fairly quick. These observations would strongly suggest that, clinically, when a residual retinal circulation is seen in OCAR, the site of occlusion is probably where the artery pierces the dura mater (i.e., the part of the artery with the narrowest lumen³¹) and in eyes with no residual circulation (except filling of the capillaries on the surface of the optic disc) the site of occlusion is likely to be in the lamina cribrosa.

EFFECT OF ISCHAEMIA ON RETINAL VASCULATURE

The present study provides important information on this subject. The findings show that acute transient ischaemia of up to 4½ hours does not produce retinal capillary obliteration, but an acute transient ischaemia of 6-7½ hours or longer can produce it.²⁷⁻²⁸ If the OCAR is permanent, no fluorescein leakage is seen at any stage.²⁷⁻²⁸

Retinal ischaemia is thought to upset the normal retinal-blood barrier in the retinal capillaries. Cunha-Vaz³² demonstrated in rats that temporary ischaemia of 70 minutes and longer increased permeability first of the retinal arterioles and later, at 24 hours, led to preferential involvement of the venous side. The permeability change was directly related to the changes in the endothelial cells and no passage of the tracer took place through the interendothelial junctions, which were always closed.³³ Reinecke *et al.*⁵ showed death of the endothelial cells and finally of the mural cells in cats after an experimental ischaemia of 1½ hours by

raised intraocular pressure. Our findings would indicate that in spite of severe endothelial cell damage by ischaemia it probably takes 2½-3 hours to produce fluorescein leakage with normal intraluminal blood pressure, and that too is only a transient phenomenon lasting at the most 4-5 days, with full recovery after that. This would also suggest that acute ischaemic damage to the retinal endothelial cells for up to 2½ hours does not seem to upset the retinal-blood barrier significantly. The subject of the retinal-blood barrier in retinal vascular occlusion is discussed at length elsewhere.²⁸

OPHTHALMOSCOPIC APPEARANCES DURING OCAR

The classical description of this by von Graefe¹ 120 years ago, and numerous other clinical reports, are essentially based on anecdotal observations, because it is very rarely that a patient comes to an ophthalmologist within an hour or two of the occlusion. There has been no systematic evaluation of the ophthalmoscopic appearances at different time intervals after the onset of angiographically confirmed OCAR in primates or man. The present study provides such information (see above) for transient retinal ischaemia up to 4½ hours, and our previous study²⁷⁻²⁸ on longer or permanent OCAR. One remarkable fact emerges from these 2 studies: *in spite of angiographically proved complete occlusion of the CAR, it was not at all uncommon to find on ophthalmoscopy normal-looking retinal vessels*, misleading an observer to believe that the retinal arteries had a normal or almost normal blood flow. This is a serious drawback in some of the observations reported in the preangiography era. *Normal-looking retinal vessels do not rule out a complete OCAR.* This study for the first time also provides us information on the resolution pattern of retinal ischaemic changes on restoration of retinal circulation.

The cherry red spot, which is pathognomonic of OCAR (Fig. 6a) is due to the normal red colour of the retinal pigment epithelium (which is mostly responsible for the normal colour of the fundus) seen through the normal avascular zone of the fovea (not supplied by retinal circulation), which is not involved by the retinal ischaemia and consequently the retinal opacity, while the surrounding opaque retina masks the normal red colour of the fundus background.

The peripheral fundus (around the posterior retina) looks normal in OCAR. In this peripheral part the retina is thin, with a thin nerve fibre layer and sparse ganglion cells, so that choroidal blood supply is probably sufficient to maintain the structural integrity of the retina.

Retinal pigment epithelial degeneration of the posterior retina was seen in all eyes with ischaemic retinal atrophy in spite of normal choroidal circulation, usually developing gradually 3 weeks after a prolonged OCAR in this study and in our previous experimental studies^{27, 28} and also seen clinically with similar lesions. The exact mechanism of the pigmentary degeneration is not known. Possibly, ischaemic destruction of the Müller cells has some role to play in this.

INFLUENCE OF RESIDUAL RETINAL CIRCULATION ON RETINAL RECOVERY/SURVIVAL TIME

Watson²⁴ very well reflected the prevailing view that if there is even a minimal retinal circulation after OCAR it is possible to obtain a considerable recovery in these eyes. The present studies clearly showed that the existence of any small residual retinal circulation after OCAR does not seem to protect the retina, presumably because of its very low oxygen tension. *The duration of the retinal ischaemia was almost always the principal determining factor in the production of irreversible retinal damage, i.e., the longer the ischaemia the more marked the retinal damage.* An occasional eye, however, showed variation from this pattern and represented a normal biological variation in response.

WHAT DOES REDNESS OF A NORMAL OPTIC DISC REPRESENT?

The present study provides important information on the subject. During OCAR the optic disc was almost always pale. The main source of blood supply to the disc is by the PCA circulation, with the retinal arteries supplying only the surface nerve fibre layer of the disc.^{25, 29} In these eyes with OCAR angiography showed perfectly normal PCA circulation and normal filling of the prelaminar part of the disc (Fig. 1a, 2a), and yet the disc was pale. Also in our recent experiments with rhesus monkeys a few minutes after all the PCAs were cut (but the CAR left intact) the optic disc remained perfectly normal in colour in the majority. A few showed some pallor, mostly of the temporal region, because of the PCA contribution to the surface nerve fibre layer capillaries in that region.^{25, 29} It appears, then, that the normal redness of the disc is essentially due to the filling of the capillaries in the surface layer of the disc and not due to its deeper vessels. This further confirms our previous observations that in a normal optic disc redness of the disc is not a true guide to its vascularity.^{25, 25}

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Swaner for his technical assistance, and to Miss Cynthia Pokorny for her secretarial help. This study was supported by the National Eye Institute grant EY-01576. Figs. 4a, 4b, and 5a, 5b are reproduced from Van Heuven *et al.*³⁰

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Visual prognosis following treatment of acute central retinal artery obstruction

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SUMMARY The authors report the visual outcome in 34 consecutive cases of treated acute central retinal artery obstruction. Visual acuity equal to or better than 6/30 was recovered in 35% of the cases. The presenting visual acuity and duration of visual impairment appear to correlate with visual prognosis.

The prognosis for useful vision after central retinal artery obstruction is generally considered poor, except in those cases in which a patent cilioretinal artery supplies the fovea.¹ Consequently various therapeutic regimens have been devised for this condition. The efficacy and limitations of many of these regimens have been reviewed in detail by flytche.² Some patients have been reported to regain useful vision after treatment.³⁻¹¹

The authors initiated a prospective but uncontrolled study of patients with spontaneous acute central retinal artery obstruction in order to evaluate their visual prognosis following treatment. This report describes our treatment regimen and relates our experience with 34 consecutive cases.

Patients and methods

All patients referred to the Retinal Vascular Unit between March 1976 and October 1978 with the diagnosis of acute central retinal artery obstruction were considered for the study. Visual acuity was recorded and a complete ocular examination, including slit-lamp biomicroscopy, applanation tonometry, and ophthalmoscopy, was performed. The affected eye was studied by fluorescein angiography and electroretinography to confirm the clinical diagnosis. The diagnosis was considered to be established only if the affected eye showed fundus features typical of acute central retinal artery obstruction, a typical fluorescein angiographic appearance, and characteristic electrophysiological responses. Patients with a fovea-sparing cilioretinal artery were excluded.

Every patient underwent treatment according to

our regimen. This treatment was begun immediately after the diagnosis had been established. The treatment¹² consisted of (1) paracentesis of the anterior chamber under the slit-lamp biomicroscope with topical anaesthesia and the use of a tuberculin syringe and 27 gauge needle; (2) controlled ocular massage using a fundus contact lens while visualising the retinal vessels at the disc; (3) inhalational therapy with a 95% oxygen/5% carbon dioxide mixture administered by mask for 10 minutes every hour during the waking hours and every 4 hours during the night; and (4) oral administration of acetazolamide (250 mg q.i.d.) and aspirin (10 grains (65 mg) b.i.d.). Every patient underwent a complete physical examination with emphasis on the cardiovascular system. A complete blood count, an erythrocyte sedimentation rate, a serum lipid profile, a fasting blood glucose, an electrocardiogram, and a chest x-ray were obtained on admission. Inhalation therapy was discontinued after 48 to 72 hours, but acetazolamide and aspirin were continued for at least 2 weeks. These drugs were then discontinued unless another indication for their continued use existed. Drugs and dosages for the associated systemic disorders were managed by the internist.

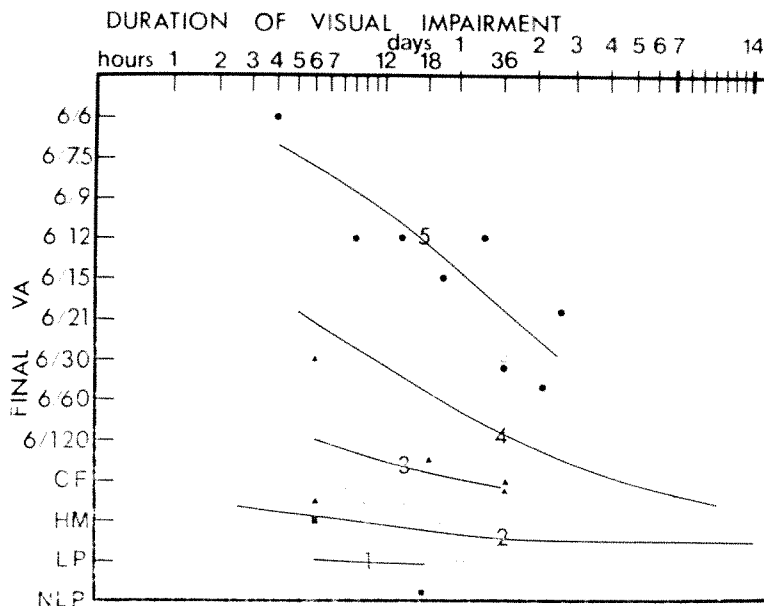
Complete ophthalmic examination was repeated prior to hospital discharge and again at follow-up 1 month or more after treatment. Early (1-2 days) and late (over 2 weeks) post-treatment fluorescein angiograms and electroretinograms were obtained in many of the cases in order to assess the changes in retinal perfusion and electrical retinal responsiveness.

Results

Thirty-two patients were included in the study. They ranged in age from 32 to 74 years, average

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Fig. 1 Graph relating duration of visual impairment (ordinate, logarithmic scale), presenting visual acuity and final visual acuity (abscissa) for 34 cases of acute central artery obstruction. The 5 lines on the graph (1-5) are isoacuity curves for presenting visual acuity corresponding to the symbols defined below. The better the presenting visual acuity, the steeper the slope of the isoacuity curve. Symbols indicate presenting visual acuity as follows: ■ NLP (line 1); ○ LP (line 2); ▲ HM (line 3); □ CF at 1 m (line 4); ● CF at 1 m (line 5).



62 years (Table 1). Twenty-five were men (78%) and 7 were women. Nineteen were white and 13 were black. The average duration of follow-up was over 2 months (67.8 days). Two patients had recurrent acute central retinal artery obstruction, making the total number of cases 34. The central retinal artery obstruction occurred in the right eye in 21 (61%) and in the left eye in 13 (39%). The presenting visual acuities ranged from 6/60 to no light perception (Table 1). The recognised duration of persistent visual impairment ranged from 2.5 hours to 2 weeks (Table 1) with a median of 19 hours.

A significant improvement in visual acuity was defined as a sustained improvement of 3 or more visual acuity gradations (Fig. 1, ordinate) and a final visual acuity of 6/30 or better on follow-up examination 1 month or more after treatment. Twelve of our 34 cases (35%) showed significant improvement in visual acuity (Table 1). Seven of our cases (21%) improved by 6 visual acuity gradations or more and achieved a final visual acuity of 6/12 or better. None of our cases had a post-treatment visual acuity worse than the presenting visual acuity. Only 9 of our 34 cases (26%) showed no improvement in visual acuity whatsoever.

Seven of the 12 cases that improved significantly had already done so within 48 hours after initiation of treatment. However, the maximal visual acuity achieved in the 12 cases that showed significant improvement was attained in only 4 within 48 hours. Further visual improvement occurred beyond 48 hours in the remaining 8 cases.

The 12 cases that achieved significant improvement in visual acuity had an average presenting visual acuity of counting fingers (CF) at a distance of greater than 1 m, whereas the 22 cases that did not improve had an average presenting visual acuity of poor hand movement (HM). The difference between these 2 groups is statistically significant ($t=3.95$, $P<0.05$). The average duration of recognised visual impairment prior to initiation of treatment in those cases that showed eventual significant visual improvement was 21.1 hours as compared to 58.6 hours in those cases that did not improve. The longest duration of visual impairment reported by any patient who showed significant visual improvement at follow-up was approximately 72 hours.

Presenting visual acuity and duration of visual impairment are related simultaneously to final visual acuity in Fig. 1. This graph presents the duration of visual impairment in a logarithmic scale on the abscissa to visual acuity on the ordinate (see legend to Fig. 1 and Discussion for interpretation of graph).

Patient age, presence or absence of clinically detected emboli, and clinical evidence of systemic disorders, including hypertension and atherosclerotic vascular disease, were evaluated for any correlation with visual prognosis. No statistically significant correlation was found between the patients who improved visually and those who did not for any of these subgroups. Nine of the 32 eyes (28%) had a non-fovea-sparing cilioretinal artery. No statisti-

Table 1 Clinical data on 34 treated cases of acute central retinal artery obstruction

Case	Age	Sex	Eye	Presenting visual acuity	Duration of visual impairment	Final visual acuity	Success (S) or failure (F)*
1	57	M	OD	LP	2 Weeks	LP	F
2	32	M	OD	6/60	20.5 h	6/15-	S
3	59	M	OD	LP	3 Days	LP	F
4**	32	M	OD	CF at >1 m	14 h	6/12-	S
5	73	M	OD	CF at >1 m	52 h	6/60+	F
6	71	M	OS	LP	24 h	LP	F
7	51	M	OS	HM	18 h	CF at >1 m	F
8	71	M	OD	LP	7.5 h	CF at <1 m	F
9	56	M	OS	LP	20 h	HM	F
10	69	F	OS	LP	26 h	HM	F
11	64	M	OD	NLP	17 h	NLP	F
12	58	M	OD	CF at >1 m	3 Days	6/21	S
13	64	M	OS	HM	6 h	6/30+	S
14	63	F	OD	CF at <1 m	5 h	6/12-	S
15	74	F	OS	CF at <1 m	10 Days	CF at <1 m	F
16	50	M	OD	NLP	6 h	HM	F
17	54	M	OD	HM	36 h	CF	F
18	72	M	OS	CF at <1 m	36 h	6/30	S
19	61	F	OS	CF at >1 m	36 h	6/30-	S
20	55	M	OD	HM	6 h	CF	F
21	63	M	OS	LP	8 h	6/9	S
22	64	F	OD	CF at <1 m	14 h	HM	F
23	59	M	OS	CF at >1 m	9 h	6/12	S
24	58	M	OD	CF at >1 m	30 h	6/12	S
25	61	M	OD	LP	36 h	CF at <1 m	F
26	64	M	OD	LP	2.5 h	HM	F
27	70	F	OS	CF at <1 m	1 Week	HM	F
28***	58	M	OD	LP	4 Days	HM	F
29	69	F	OD	LP	12 Days	CF	F
30	66	M	OD	CF at <1 m	8 h	HM	F
31	64	M	OD	HM	36 h	CF at <1 m	F
32	48	M	OD	CF at >1 m	4 h	6/6	S
33	70	M	OS	CF at <1 m	12.5 h	6/7.5	S
34	74	M	OS	CF at <1 m	10 h	CF at <1 m	F

*Success (S) and failure (F) as defined in text. **Same patient as case 2; reobstruction of central retinal artery OD. ***Same patient as case 24; reobstruction of central retinal artery OD.

cally significant correlation could be found between the presence or absence of such arteries and recovery of visual acuity after central retinal artery obstruction.

The b wave amplitude in the affected eyes evaluated by pretreatment electroretinography was less than in the respective fellow eyes in every case by a proportion ranging from 16 to 46%. The a wave amplitude of the affected eyes ranged from 32% less than to 12% greater than that of the respective fellow eyes. The ratio of b wave amplitude to a wave amplitude (b/a ratio) was consistently less in the affected eyes (average 1.29) than in the respective fellow eyes (average 1.68). The group of patients who achieved significant improvement in visual acuity had average reductions of b wave amplitudes and levels of b/a ratios in the affected eyes that were markedly less than those of the group of patients who did not improve visually (19.5% average b wave reduction, 1.46 average b/a ratio in improved cases; 41.7% average b reduction, 1.24 average b/a ratio in unimproved cases).

Pretreatment fluorescein angiograms of our patients showed that none of them had total obstruction of flow into the affected eye via the central retinal artery, in spite of the clinical features indicative of central retinal artery 'occlusion'. Similar observations of the infrequency of demonstrable total obstruction of the central retinal artery by fluorescein angiography in such cases have been reported previously.¹³ On the other hand all our patients studied by pretreatment fluorescein angiography showed delayed retinal arterial filling and a prolonged interval between initial choroidal flush and retinal arterial filling. Furthermore, some of the angiograms showed evidence of abnormal choroidal filling as well.

Comments

Our results suggested that the prognosis for visual acuity in acute central retinal artery obstruction may not be as dismal as previously believed.

The observation that some of our patients recovered a significant degree of visual acuity indicates that these patients had at least partially reversible impairment of retinal function at the time of presentation. The degree of reversibility appeared to correlate with presenting visual acuity and duration of visual impairment. Fig. 1 shows the interrelationship between these 2 factors and final visual acuity in our 34 cases. The curves on the graph indicate the projected average final visual acuity for eyes with treated acute central retinal artery obstruction separated into 5 levels of presenting visual acuity. In patients with severe visual impairment at

presentation (visual acuity light perception or worse, lines 1 and 2 in Fig. 1) the likelihood of significant improvement in visual acuity appears to be small even if the duration has been only 2-4 hours. In contrast the average patient with relatively good presenting vision (visual acuity $\geq$ counting fingers at 1 m, line 5 in Fig. 1) can attain a final visual acuity of approximately 6/30 even after a duration of 36-48 hours.

The precise relationship between presenting visual acuity and the degree of impairment of blood flow into the eye via the central retinal artery is not known. Experimental total central retinal artery obstructions in rhesus monkeys of up to 90 minutes' duration have been shown to cause no persistent ophthalmoscopic, angiographic, electrophysiological, or morphological damage to the retina.¹⁴ Nonperfused retina in monkeys and cats appears to survive central retinal artery occlusion for prolonged periods because of the metabolic contributions of the intact choroidal circulation to the retina.¹⁵ Partially perfused retina, which appears to be present in almost all human clinical cases of central retinal artery obstruction,¹³ is probably able to survive in a reversible preinfarction state for a much longer period of time. Restoration of the central retinal artery blood flow, either spontaneously or in response to therapy, permits recovery of visual acuity to a level determined by the viability of the retina at that time. Reduction of the functional severity of the central retinal artery obstruction therapeutically, by means such as abrupt lowering of the intraocular pressure by paracentesis and increasing the retinal oxygenation by inhalation therapy with 95% oxygen and 5% carbon dioxide, may prolong the period of retinal viability in a preinfarction ischaemic state. Such treatments may, in effect, provide time for the retinal arterial circulation to undergo alterations that improve retinal perfusion by bypassing or reopening the obstructed artery.

The prognostic significance of the actual recorded a and b wave voltages on the electroretinograms in our cases was difficult to assess. A considerable overlap existed between the range of voltages in the 'normal' fellow eyes and that of the affected eyes. This difficulty has been alluded to previously by Henkes,¹⁶ who noted that only 22% of his patients with central retinal artery obstruction had a normal ERG in the unaffected eye. The prognostic significance of fluorescein angiographic intervals was also difficult to assess. We encountered problems of reproducibility in measurement of the various angiographic intervals. Because of these difficulties, we have not found these studies particularly useful as prognostic indicators of the likeli-

hood of significant visual recovery in our patients. However, the value of these studies as prognostic tools is still being evaluated.

We have attempted to compare the visual recovery rate of our patients with that reported by other investigators.

Lorentzen¹⁷ reported that none of his 12 cases of central retinal artery obstruction (treatment not specified) showed significant visual improvement (by our criteria). Karjalainen¹⁸ reported long-term follow-up of 53 patients with prior acute central retinal artery obstruction. Ten of the 53 cases (19%) showed significant visual improvement (by our criteria). However, 12% of the eyes had a patent cilioretinal artery. Henkes¹⁶ reported that 5 of his 19 cases (26%) with visual acuities recorded for both presenting and follow-up examinations showed significant visual acuity improvement (by our criteria) after treatment with intravenous and oral vasodilators. He did not state whether or not any of his cases had a fovea-sparing cilioretinal artery, which is known to improve the visual prognosis.¹

Brown and Shields¹ reported on the prevalence and prognostic implications of a patent cilioretinal artery in a retrospective study of acute central retinal artery obstructions. Among their 107 patients 28 (26%) had a patent cilioretinal artery in the affected eye. In 5 of these 28 cases less than half the papillomacular bundle was supplied by the patent cilioretinal artery. Not one of these cases showed significant visual improvement or achieved a visual acuity better than counting fingers. In 11 of these 28 cases the patent cilioretinal artery supplied more than half of the papillomacular bundle but did not spare the fovea. The follow-up visual acuities in these cases ranged from 6/30 to counting fingers. Twelve of their cases had a fovea-sparing cilioretinal artery. All but one of these cases achieved a final visual acuity of 6/30 or better. The authors commented that in acute central retinal artery obstruction with a fovea-sparing cilioretinal artery, 'there is about a 91% chance that eventual visual acuity will be in the range from 6/6 to 6/24 and about an 83% chance it will range from 6/6 to 6/15'.

Conclusion

This uncontrolled study does not prove the efficacy of our treatment regimen. Without a double-masked controlled study one is unable to exclude the possibility that several or all of our cases that showed significant visual improvement after treatment might also have improved without treatment. The incidence of spontaneous, significant improvement in visual acuity after central retinal artery obstruction

is unknown. However, it is well known that occasional cases of acute central retinal artery obstruction without a fovea-sparing cilioretinal artery show a marked recovery of visual acuity without treatment. The authors recognise that further investigation is needed to clarify the efficacy of treatment in these cases. However, we can conclude from our study that a completely dismal prognosis for recovery of useful vision in eyes with acute central retinal artery obstruction is probably unwarranted.

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Central retinal artery occlusion following cosmetic blepharoplasty

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SUMMARY A case is presented of a 70-year-old white male who underwent a bilateral cosmetic lower lid blepharoplasty with fat removal. He subsequently developed a right orbital haemorrhage which resulted in the occlusion of the central retinal artery. The patient had no light perception with his right eye for approximately 1 hour, but vision was eventually restored to 20/20 after emergency therapeutic measures. There are many possible causes of visual loss following blepharoplasty, with orbital haemorrhage being the most common. Visual loss secondary to blepharoplasty can be prevented in the preoperative, intraoperative, and postoperative phases of surgery. Blindness as a complication of cosmetic blepharoplasty can be reversible if recognised early and treated appropriately. These facts must be kept in mind by all surgeons who perform blepharoplasties.

Blindness following cosmetic blepharoplasty is rare. According to DeMere's survey of 3000 physicians performing blepharoplasties¹ the occurrence was 0.04% or 1 case per 2500 operations. In 1969 Smith² reported that visual loss following blepharoplasty was rarely encountered as a complication of blepharoplasty. Castanares³ reported that he had seen only 1 case of blindness following blepharoplasty, but had seen at least 40 cases of unilateral partial blindness during his 25 years of practice. Jafek⁴ reported one case of unilateral blindness attributed to an intraorbital haemorrhage following blepharoplasty with fat excision. His review of the medical literature revealed no case reports for such an occurrence over the previous 5 years. Putterman⁵ reported the case of a patient who suffered complete unilateral blindness following blepharoplasty with fat excision. With therapeutic intervention the affected eye of this patient was returned to its preoperative visual acuity with no apparent sequelae.

Hueston and Heinze⁶ discussed the early diagnosis and surgical reversal of a case of blindness following blepharoplasty. They later reported a similar case of blindness reversed by wound decompression.⁷ They concluded that outpatient blepharoplasty procedures were 'intrinsically unsafe' and recommended close inpatient supervision postoperatively.

Blindness following orbital surgery other than blepharoplasty was reported by Long and Ellis⁸ in 1971. Eight cases were described which followed orbital exposure by Berke-Krönlein technique. Blindness has also been described following reduction of fractured zygoma,⁹ the repair of orbital floor fractures,¹⁰ retinal detachment procedures,¹¹ and neurosurgical procedures.¹²

The most recent literature review and discussion of blindness following blepharoplasty was by Waller.¹³ He concluded that blindness is a rare but real complication of blepharoplasty which must be considered by the physician performing this operation.

Case report

A 70-year-old white male underwent bilateral cosmetic upper lid blepharoplasties with fat removal. Six weeks later he was scheduled to undergo cosmetic bilateral lower lid blepharoplasties, also with fat excision. His preoperative examination included a visual acuity of 20/20 in both eyes and was otherwise completely normal except for dermatochalasis of both lower lids. He had no history of hypertension or any other medical problem and was receiving no medication.

The procedure performed was a standard bilateral lower lid blepharoplasty under local anaesthesia as described in the AAOO manual on ophthalmic plastic surgery.¹⁴ Fat excision was performed without

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Fig. 1 Four hours following bilateral lower lid blepharoplasties with fat excision. There has been a right orbital haemorrhage with proptosis, subconjunctival haemorrhage, chemosis, and periorbital oedema. Vision is no light perception with the right eye and 20/20 with the left.

difficulty. The fat presented easily and haemostasis was achieved by cauterising the cut end of fat before releasing the haemostat. The orbital septum was not sutured. Haemostasis appeared adequate at the end of the procedure. A small pressure patch was placed over both infraorbital rims, leaving the eyes uncovered. The patient was instructed to remove the patches on arriving home and to apply ice packs intermittently over both lower lids.

The patient began to notice right orbital pain and significant swelling of the right lower lid 2 hours after surgery. He returned to the ophthalmology clinic about 4 hours after surgery. He stated that he had been unable to see light with his right eye for more than 1 hour before returning to the clinic. He had also experienced severe pain of his right eye during that time.

The initial evaluation revealed marked proptosis of the right eye with extensive subconjunctival haemorrhage, chemosis, limited motility, and periorbital oedema (Fig. 1). The right eye was hard to finger palpation, and the intraocular pressure was over 60 mmHg measured with a Schiøtz tonometer with a 15 g weight. The right eye had no light perception. The right pupil was not reactive to light but was reactive consensually to light to the left eye and to a near stimulus. Direct and indirect ophthalmoscopic examination of the right eye revealed no perfusion of blood through the central retinal artery or its branches and stagnation of blood in the venous system.

Immediate therapeutic measures were instituted. Initially a right lateral canthotomy was performed. The right lower lid suture line was then opened and approximately 10 ml of blood under pressure was

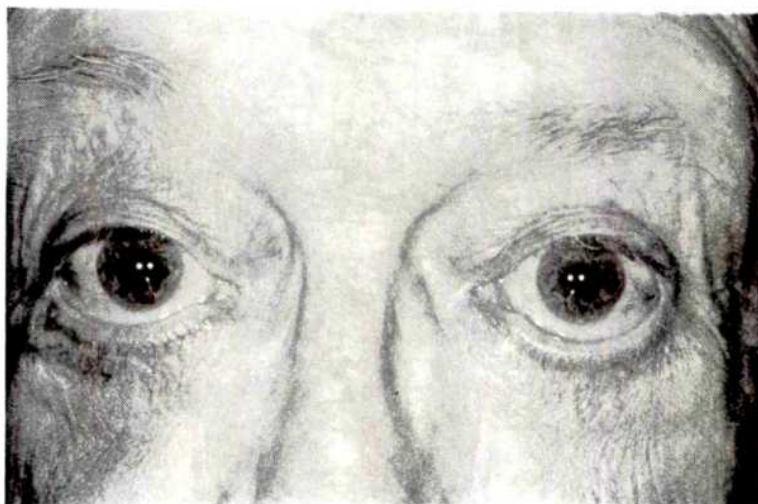
released. A 3 ml retrobulbar injection was given consisting of equal parts of lidocaine HCl 2%, hyaluronidase, and aminophylline. An additional 2 ml of hyaluronidase was injected into the swollen right lower lid. Intermittent digital massage was applied to the right eye. An intravenous drip was started and 500 mg of acetazolamide was given rapidly followed by 25 g of mannitol over 3 minutes. No additional mannitol was given. An additional 250 mg of acetazolamide was given intravenously every 6 hours for the next 24 hours. Bag rebreathing was started with the patient in the supine position until carbogen (5% CO₂, 95% O₂) became available. Carbogen was administered with continuous monitoring of the patient's pulse, respirations, and blood pressure for 10 minutes every hour for 12 hours.

After these measures were performed 15 minutes had passed and the intraocular pressure was 38 mmHg with a Schiøtz tonometer with a 10 g weight. Ophthalmoscopy revealed perfusion of the entire retina at that time without apparent occlusion of any portion of the retinal artery system. Within 30 minutes the temporal half of the patient's right visual field returned increasing to a full visual field to confrontation within 1 hour after treatment was begun. At that time the patient's vision with his right eye was 20/200 with a near card.

Gentamicin 80 mg intramuscularly every 8 hours and methicillin sodium 2 mg intravenously every 6 hours were started and continued for 72 hours. After drainage from the lower lid wound ceased at 48 hours, a retroauricular skin graft was used to close the wound.

The visual acuity in the right eye improved to

Fig. 2 Ten months after the central retinal artery occlusion. A satisfactory cosmetic result has been achieved. Vision is 20/20 with both eyes.



20/60 by 48 hours and to 20/20 within 72 hours of treatment. Visual field perimetry in the right eye showed slight constriction of the central isoptre at 24 hours, but reverted to normal within 48 hours. The patient's vision was 20/20 in the right eye with a full visual field 10 months after the central retinal artery occlusion. A good cosmetic result was also achieved on his right lower lid (Fig. 2).

Discussion

Various mechanisms have been proposed as the cause of visual loss following blepharoplasty. Most authors feel that increased intraorbital pressure is a major factor, whether it is a result of orbital haemorrhage or oedema as a result of operative manipulation. Hepler *et al.*¹⁵ felt that sudden or complete loss of vision following blepharoplasty was caused by (1) orbital haemorrhage causing increased orbital pressure which compromised the vascular circulation within the eye; (2) acute angle-closure glaucoma in susceptible individuals; or (3) optic nerve ischaemia, possibly due to orbital manipulation and/or pressure or secondary systemic hypotension from preoperative medications. Also all the cases of visual loss following blepharoplasty which he and others¹³ reported have been associated with fat removal at the time of surgery.

Putterman⁵ proposed additional causes for orbital haemorrhages: (1) eyelid neovascularisation secondary to retinal detachment repairs; and (2) rebound vasodilatation from epinephrine-constricted vessels escaping cautery during surgery. Another commonly reported cause of orbital haemorrhage is excessive tugging on orbital fat during excision. Inadequate haemostasis of excised fat by failure to adequately

cauterise the cut ends can also lead to orbital haemorrhage. Other contributing causes to orbital haemorrhage are bleeding diatheses or severe arteriosclerosis.

The usual mechanism of visual loss is increased intraorbital pressure producing a central retinal artery and/or vein occlusion, or causing direct pressure on the optic nerve with subsequent occlusion of its vascular supply. Total vascular insufficiency for 60–120 minutes produces permanent loss of vision.⁷ A lesser duration of occlusion leads to variable visual recovery. Clinically the signs and symptoms of orbital haemorrhage are an acute onset of orbital pain with an increased intraorbital pressure manifested by proptosis, lid ecchymosis, increased intraocular pressure, limited extraocular muscle movement, and a dilated, unresponsive pupil. Visual acuity is usually reduced but can range from 20/20 to no light perception. The clinician should be familiar with these signs and symptoms so that he may act quickly and definitively should they appear.

The treatment of orbital haemorrhage as shown by the above signs and symptoms varies according to the author. If no visual loss has occurred and vision does not appear threatened, close observation of visual acuity, intraocular pressure, and fundus vessel perfusion may be all that is required. However, when evidence of acute or impending decreased retinal perfusion occurs, immediate therapy must be initiated. If the surgeon caring for the patient is not an ophthalmologist, immediate assistance from a qualified ophthalmologist should be obtained while emergency measures are being instituted.

A lateral canthotomy can be performed easily to decrease intraorbital pressure. The surgical wound

should also be opened and the haematoma evacuated. A search for the bleeding site should be performed.

An intravenous drip should be started and 20% mannitol solution should be given as a bolus of 12.5 g (62.5 ml) over an initial 3–5 minute interval, followed by a slower administration of additional mannitol solution to achieve a total dose of 1 g/kg of body weight over the next 30 minutes.¹⁶ Intravenous acetazolamide (500 mg) is given as an intravenous push bolus with an additional 250 mg given intravenously every 6 hours for at least the first 24 hours. Digital ocular massage may be helpful to decrease intraocular pressure while awaiting action of the intravenous osmotic agent. The patient should be placed horizontally and made to rebreathe in a small paper bag (a classic lunch bag size is best) until a mixture of 95% O₂/5% CO₂ (carbogen) can be obtained for intermittent breathing. Carbogen is available from most pulmonary therapy laboratories. The injection of retrobulbar xylocaine and aminophylline can be performed to promote dilation of the central retinal artery. The efficacy of this treatment has not been definitively proved and is not universally recommended. Hyaluronidase is added to promote diffusion of the xylocaine and aminophylline through the orbital tissues. The hyaluronidase also greatly enhances the reabsorption of fluid from the orbital tissues.¹⁷

Paracentesis of the anterior chamber has been advocated to reduce intraocular pressure,¹⁶ but this is a hazardous procedure and should be performed only by an ophthalmologist experienced in the technique.¹⁸ Intraocular haemorrhage, cataract formation, and iris prolapse are only 3 of the possible complications which can result from a paracentesis.

Systemic antibiotics should be started after opening of a surgical wound for the evacuation of a haemorrhage. The wound should be closed again only after drainage has ceased.

During the acute treatment phase the patient should be carefully monitored with visual acuities, pupillary response, funduscopy, and confrontation visual fields to assess the response to therapy. After the immediate therapy has ceased the visual acuity and visual fields should be examined and recorded.

The prevention of orbital haemorrhage with subsequent visual loss can be grouped into 3 categories: preoperative, intraoperative, and postoperative.¹⁹

(1) PREOPERATIVE

Moser *et al.*²⁰ reported nonsurgically related postoperative blindness following blepharoplasty surgery. They emphasised the need for preoperative

examination and recording of visual acuity and other unassociated ocular pathology. DeMere *et al.*¹ found that adequate eye examinations were performed in only 50% of patients undergoing eyelid surgery. This ranged from a high of 90% in ophthalmologists to 15% for plastic surgeons. Amblyopia is present in about 2% of our population, and coexistent eye disease in patients undergoing eyelid surgery is a distinct possibility which must be ruled out, for example, cataract, glaucoma, old trauma or scar, or retinal detachment. Patients often do not realise that one eye is blind until the opposite eye is closed or covered. Discovering this immediately after surgery, even though it was pre-existent, causes the patient to relate the decreased visual acuity to the surgery itself.

A good drug history should be obtained with particular emphasis on vasodilators, aspirin, warfarin sodium, and other blood coagulation altering agents. An evaluation for arteriosclerosis and hypertension should also be performed. Any eye abnormalities should be noted and recorded if possible with photographs. One should rule out thyroid or renal disease as causes for lid abnormalities.¹⁹ A surgeon should be hesitant to perform blepharoplasty with fat removal in a one-eyed patient unless it is definitely indicated. A history of a true allergy to local anaesthetics obviates their use during blepharoplasty and general anaesthesia is indicated instead.

(2) INTRAOPERATIVE

During the operative procedure care must be given to meticulous dissection, atraumatic tissue handling, and complete haemostasis. Undue traction on the orbital contents, especially during fat removal, can lead to orbital haemorrhage. Fat removal must be limited to that fat which presents itself through the orbital septum with only light pressure on the globe. The orbital septum should not be excessively opened to obtain orbital fat. When excising orbital fat, a clamp should be placed on the fat, the fat excised with scissors (to leave a larger stump on the clamp for cauterisation), and cauterisation carried out with a hot wire or bipolar cautery. Cautery should be used with care anterior to the orbital septum and never intraorbitally. Electrocoagulation by diathermy is not thought to be adequate for haemostasis. When the fat has been cauterised, the clamp should then be opened and the distal stump of fat examined for bleeding with additional cautery as necessary. Before closing the wound a dry field is essential to avoid complications. If epinephrine is used with the local anaesthetic, care must be exercised that postoperative rebound vascular dilatation does not occur in a previously dry field.

Avoidance of inadvertent excessive pressure on the globe should be practised. Hollenhorst *et al.*¹² reported that central retinal artery occlusions can occur during cervical neurosurgical procedures as a result of the head rest causing inadvertent ocular pressure. If an eye is covered during any surgical procedure, a protective metal shield must be properly placed over the eye to prevent inadvertent pressure.

(3) POSTOPERATIVE

Postoperative pressure dressings are mentioned only to be condemned. Pressure increases as reported by Jarrett and Brockhurst¹¹ do occur with elastic bandages over the eyes and can contribute to vascular compromise. Pressure dressings obscure observation needed to detect decreasing visual acuity, increasing intraocular pressure, and signs of orbital haemorrhage or other increases in orbital pressure. If an orbital haemorrhage occurs, pressure dressings raise the intraorbital pressure to much higher levels than if no patch were present. Many authors feel that blepharoplasty with fat removal should not be done unless careful postoperative observation is possible, meaning hospital admission in most cases.

During the first 2 hours postoperatively visual acuity assessments and observation for pain or proptosis should be performed every 10 minutes. The intervals can be lengthened to every 4 hours from 2 to 24 hours after surgery. The examination must be performed by qualified medical observers. A gauze pad soaked in iced or chilled saline can be loosely applied over the eyes for the first 24 hours to decrease swelling.

Should signs or symptoms of an orbital haemorrhage occur, the surgeon should be contacted immediately. If decreasing visual acuity is found secondary to the suspected orbital haemorrhage, emergency treatment measures should be immediately instituted as outlined above. If visual loss is reversed, careful monitoring of the patient's visual status is necessary including visual acuity, pupillary reaction, fundus examination, and visual fields until the patient's condition is entirely stable.

Dr John W. Shore and Dr Hal C. Hudson, Captain Marsha Yeager Sherry, and Lieut. Nancy Wylie provided invaluable assistance during the emergency care of this patient.

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Mechanism of rotatory eye movements in opsoclonus

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SUMMARY 'Rotatory nystagmus', in which the visual axis of the eye moves involuntarily in the horizontal and vertical planes describing a closed loop trajectory, was analysed by means of combined video and electro-oculography in a patient with multiple sclerosis having numerous ocular signs of cerebellar disease. The rotations were sporadic, isolated single cycles having stereotyped, crescentiform loop shapes. Each consisted of a combination of a single cycle of vertical ocular flutter, the onset of which was followed 40 to 50 milliseconds later by a single cycle of horizontal ocular flutter. The timing relationship between flutters suggest that the vertical and horizontal systems had become somehow entrained. Rotatory nystagmus is saccadic in nature and arises from a unique timing relationship between vertical and horizontal flutter.

Ocular 'flutter' and opsoclonus (or 'saccadomania') are involuntary, abnormal eye movements which can occur with lesions localised to the cerebellar system and when the cerebellum is involved in a more generalised pathological process such as encephalitis.¹⁻³ Flutter has the appearance of a rapid to and fro movement of the eye which looks like a rapid tremor. Eye movement recordings show that flutter consists of a sequence of saccades in alternating directions with no intersaccadic latency. Opsoclonus takes the form of multiple saccadic eye movements in random directions, including along the oblique axes.

There is a further involuntary movement occurring in association with the above ocular signs in which the eye appears to rotate quickly as if it were tracking around the perimeter of a disc. This may be referred to as rotatory nystagmus (as opposed to torsional nystagmus, in which the eye rotates about the visual axis) and is usually classified as opsoclonus, although it is not obviously saccadic in nature. We have recorded and analysed rotatory nystagmus in a patient with a predominately cerebellar syndrome and found that the movement consists of a combination of cycles of flutter in the vertical and horizontal axes, with particular phase and velocity characteristics which determine a curved (crescentiform) trajectory.

Case history

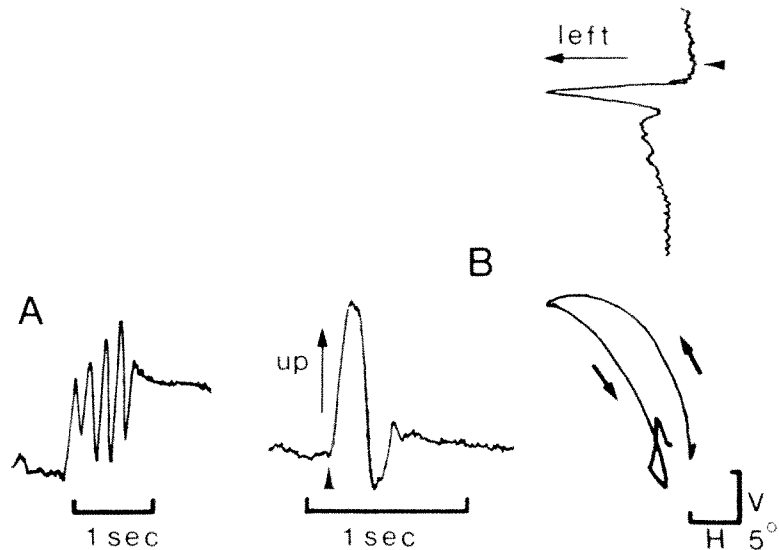
The patient was a 27-year-old male under the care of Professor John Marshall. He had progressive

neurological symptoms without remission for 4 years, commencing with vertigo on upgaze, which had been persistent. Two years prior to recording he developed disabling oscillopsia, and during the last year he had developed progressive cerebellar ataxia of all limbs in association with intermittent paraesthesia in both legs below the knees. There was no significant past family history or past medical history.

On examination of the general systems there were no abnormal findings. He was normotensive. His gait was grossly ataxic. There was obvious intellectual impairment and a dysarthria of cerebellar type. He had persistent titubation of the head at rest. He had a long-standing amblyopic right eye with vision corrected to 6/12 right and 6/6 left. There was a bilateral pendular nystagmus in the horizontal plane which was present in primary gaze and greater in the left eye. Superimposed on the pendular nystagmus were square-wave jerks in both horizontal and vertical directions. Eye movements in the direction of left gaze were dysmetric, and a mild, low-amplitude, left-beating nystagmus replaced the pendular oscillations. There was a mild decentering dysmetria to right gaze together with occasional bursts of macrosaccadic oscillations in the horizontal plane and of flutter in both the horizontal and vertical directions. Pursuit and optokinetic nystagmus were broken during following movements to the left. There were occasional stereotyped rotatory movements in which the globe moved upwards from the midposition and then towards the left, returning downwards and towards the right. These occurred on an average of 1 or 2 per

Fig. 1 A: An example of flutter-like oscillations in the vertical plane. The flutter consists of 4 cycles of to and fro saccadic movements with no intersaccadic interval. The flutter appeared to be triggered in some way by the initial upwards eye movement.

B: An example of rotatory nystagmus. The central Lissajous figure represents the vector sum of movements of the visual axis of the eye in the horizontal (H) and vertical (V) directions. This is what is 'seen' when the eye is examined. Movements in the vertical plane are shown on the left and in the horizontal plane are as shown above. The arrowheads on the Lissajous figure show the direction in which the eye rotated. The arrowheads on the vertical and horizontal eye movement components indicate the synchronisation of the two traces.



minute. Electro-oculography revealed a mild left internuclear ophthalmoplegia which was not obvious upon examination. There was mild bilateral facial weakness. The lower cranial nerves were normal. All limbs were mildly spastic, but power was normal. The deep tendon reflexes were bilaterally pathologically increased, the abdominal reflexes were absent, and the plantar reflexes were flexor. There was severe ataxia of all limbs, mainly dysmetric in type and evoked particularly on finger-nose testing. Rapid repetitive movements of hands and feet were severely impaired.

The investigation results supported the clinical diagnosis of demyelinating disease. The visual evoked potentials (VEPs) in the clinically more normal eye showed clear delay in latencies, the cerebrospinal fluid which was obtained at lumbar puncture was at normal pressure and without cells but with a protein of 105 mg/100 ml (1.05 g/l) with typical oligoclonal pattern on polyacrylamide-gel electrophoresis. The skull x-rays were normal, and the unenhanced CT brain scan was within normal limits.

Conclusions: Multiple sclerosis with predominantly cerebellar system involvement, particularly evident in the ocular signs.¹

ELECTRO-OCULOGRAPHIC ANALYSIS

Recordings of eye movements in the horizontal and vertical planes were obtained by direct coupled electro-oculography. The wave forms were displayed on an electrostatic chart recorder and on an oscillo-

scope screen. The traces on the oscilloscope screen were viewed with a video camera and superimposed on a video picture of the patient's eyes with a video mixer. This enabled us to select samples of rotatory nystagmus and verify that the associated traces were free from artefacts.

A relatively unusual feature of our patient's ocular movements was that he produced flutter eye movements in the vertical plane. These we believe have not been hitherto reported with objective recordings, and a typical example of their occurrence is presented in Fig. 1A. The beats of flutter were always initiated by movement in the vertical direction.

Electro-oculographic recording of the rotatory nystagmus is presented in Fig. 1B. The central Lissajous figure represents the path of rotation of the visual axis of the eye in the transverse plane and is the vector sum of the movements along the horizontal axis, as shown above, and along the vertical axis, as shown on the left. In fact the trajectory followed by the globe during a cycle of rotatory nystagmus was crescentiform and not circular. The vertical and horizontal traces show that the crescentic rotation is composed of synchronised single beats of flutter in the horizontal and vertical directions.

It is only by virtue of certain phase and velocity relationships between the horizontal and vertical flutter that the resultant trajectory of the eye was crescentiform. In the first place the vertical movements always began between 40 and 50 milliseconds before the horizontal movement, resulting in the

movement being predominantly upwards initially and then obliquely as the horizontal movement developed. The net result was that the eye followed the trajectory of the upper curve of the Lissajous figure. Also, there was a delay of about 20 milliseconds between the upwards and downwards saccade, so that despite the latency difference in initiation the downwards and inwards movements were synchronised and of similar velocity, with the result that the eye followed the fairly linear trajectory of the lower curve of the Lissajous figure.

All such eye movements in our patient were of this form. Although they could have been formed by coincidental synchronisation of vertical and horizontal flutter, we formed the strong impression that each occurrence of rotatory nystagmus was a distinct entity, as if the horizontal and vertical systems were coupled such that certain vertical movements would trigger off horizontal ones. We did not record any movements with a more circular trajectory, although there is no *prima facie* reason why they could not occur.

We have demonstrated that rotatory nystagmus in cerebellar disease consists of synchronised beats of flutter occurring in the horizontal and vertical axes of eye movement. The movement is crescentic

in shape because of the timing relationships between the beats of flutter along the 2 axes. This demonstration indicates that rotatory nystagmus should be classified with flutter and opsoclonus.

One curious aspect of rotatory nystagmus is that it is *not* similar to a normal saccadic movement along an oblique axis, in which case the initiations of the horizontal and vertical components of the movement are virtually simultaneous. On the contrary, the delay of 40 milliseconds or more between the vertical and horizontal saccades which make up the rotatory nystagmus suggests that an unusual entrainment has developed between the vertical and horizontal systems such that a certain type of vertical movement 'triggers' a stereotyped response in the horizontal plane.

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Study of congenital nystagmus: optokinetic nystagmus

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SUMMARY A severe defect of optokinetic nystagmus (OKN) was found in 46 patients with congenital nystagmus. Abnormal patterns of OKN, such as superimposition of pendular oscillations on the optokinetic slow component and inversion of OKN, were observed. Optokinetic gain (eye movement velocity/drum velocity) was decreased compared to that in normal subjects, and optokinetic after-nystagmus, or transient persistence of OKN after cessation of visual stimulation, was absent. These findings suggest that there is a defect in the subcortical optokinetic system in congenital nystagmus. Optokinetic responses did not clearly differentiate patients who had ocular lesions that impair vision, such as ocular albinism and opacities of the ocular media, from patients who did not have such lesions. Similar abnormal patterns of OKN were found in both groups of patients, although optokinetic gain tended to be lower in patients with ocular lesions than in those without lesions.

Optokinetic nystagmus (OKN) is a jerk nystagmus that is usually induced by movement in a large area of the visual surround during clinical examination of eye movements. Rotation of patterns, such as vertical stripes that occupy most or all of the visual field, produces movement of images across the retina. The slow component of OKN tracks the movement of the pattern and tends to stabilise images on the retina. During naturally occurring head movements the visual surround is stationary, and movement of the eyes produces movement of images on the retina. The vestibulo-ocular response (VOR) that is induced by the head movement produces a slow component in the direction opposite to that of the head movement and, therefore, decreases movement of images on the retina. However, at low frequencies of rotation (less than 1 Hz) the VOR alone cannot match the velocity of the head movement and cannot completely stabilise the retinal images. Head movements, by producing movement of images on the retina, also induce an optokinetic response. The slow components of the VOR and optokinetic response are in the same direction and act synergistically to match the velocity of the head movement and more effectively stabilise the retinal images improving vision.

Congenital nystagmus is an ocular motor disorder in which instability of fixation is manifested as

involuntary oscillations with pendular and complex wave forms.^{1,2} Its aetiology is essentially unknown. A clinically useful classification of congenital nystagmus based on its pathophysiology is not available. Previous attempts to construct a classification have divided patients into those who had associated ocular lesions, such as ocular albinism and opacities of the ocular media, and those who did not have such lesions. It was proposed that poor vision produced by ocular lesions in the first group led secondarily to instability of fixation, whereas in the second group there was a primary maldevelopment of the ocular motor system. However, there is no difference in nystagmus waveforms between these 2 groups of patients to substantiate this classification.² Careful clinical examination is the most effective means of identifying associated ocular lesions. In this study we attempt to determine if OKN differs between patients with associated ocular lesions and those without such lesions. Poorly formed, absent, and inverted OKN have been reported in congenital nystagmus.³⁻⁷ However, study of these responses with eye movement recordings has not been reported in a large number of patients.

Patients and methods

PATIENTS

Forty-six patients with congenital nystagmus were studied. Each patient received a neuro-ophthalmic examination to measure visual functions, such as

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visual acuity in the position of gaze with least nystagmus (null position), and to detect associated ocular lesions that could impair vision, such as ocular albinism, chorioretinal scars, and optic atrophy. Twenty-eight patients had no other associated ocular lesion that could impair vision and were classified as having *motor-defect* nystagmus, as described by Cogan.⁴ Visual acuity ranged from 20/25 to 20/60 in this group of patients (average 20/40). Eighteen patients with ocular lesions were classified as having *sensory-defect* nystagmus. Their visual acuity ranged from 20/40 to 20/400 (average 20/100).

EYE MOVEMENT RECORDINGS

Horizontal eye movements were recorded monocularly with a D-C electro-oculographic system that had a band width of 0–35 Hz (–3 dB). Skin electrodes were placed at the inner and outer canthi of each eye. Electrodes were also placed above and below the left eye to detect artefacts from eyelid blinks. Patients were seated within a 2-metre diameter optokinetic drum whose interior consisted of 2.5-cm wide, white, vertical stripes that were placed every 15 degrees against a black background. Patients were instructed to fixate stripes as they passed in front of them and not to track individual stripes as they traversed their visual fields. The drum was rotated at constant velocities of 10°, 30°, and 60°/second toward the right and left, and sinusoidally at 0.05 Hz and peak velocities of 30° and 60°/second. The mean slow component velocity was calculated for approximately 60 seconds (80 to 120 nystagmus cycles) by a laboratory computer after digitisation at 200 samples/second. Eye movements were also recorded during attempted fixation of a small spot in the primary position and in eccentric, horizontal positions at every 5 degrees to 30 degrees. The effects of eccentric gaze on nystagmus characteristics, such as waveform and slow component velocity, were compared to eye movements induced by optokinetic stimulation to verify that the OKN recorded was not simply the result of eccentric gaze.

The gain of the optokinetic response (slow component eye velocity/drum velocity) was then calculated. There is difficulty in attempting to measure OKN quantitatively in congenital nystagmus. The calculation of gain assumes that the movement of the drum is an accurate representation of the movement of images on the retina which is the stimulus for OKN. In congenital nystagmus, however, the spontaneous nystagmus also produces movement of images on the retina. Fortunately the movement of the drum was in one direction and was of constant velocity, while the smooth movements of the

spontaneous nystagmus were usually in both directions and had varying velocity, making detection of an effect of optokinetic stimulation easier. An experimental paradigm could be constructed in which retinal images are stabilised during spontaneous nystagmus by a negative feed-back system that detected the nystagmus and moved the drum to match the eye movements. A constant-velocity drum movement could be added, and an 'open-loop' gain of OKN could be measured. However, in the present study without retinal stabilisation the calculated 'gain' was probably a useful approximation of the function of the optokinetic system and was a closer approximation to more commonly used clinical tests of OKN.

The optokinetic response in normal subjects is characterised by a persistence of nystagmus in the dark for several seconds after optokinetic stimulation has been stopped (optokinetic after-nystagmus), and by an illusion of self-rotation in the opposite direction to drum rotation during constant velocity optokinetic stimulation (circularvection).^{8–10} An attempt was made to induce optokinetic after-nystagmus (OKAN) in 20 patients with motor-defect nystagmus and in 12 patients with sensory-defect nystagmus. After 60 s of drum rotation at a constant velocity of 60°/s optokinetic stimulation was terminated by turning off the lights and a transient persistence of OKN was sought. Sixteen patients with motor-defect nystagmus and 10 patients with sensory-defect nystagmus were questioned about circularvection. During 1 minute of constant velocity drum rotation at 60°/s patients were asked if they felt that they were moving, and, if so, in what direction they were rotating. After cessation of optokinetic stimulation in the dark they were asked if the illusion of self-rotation persisted (post-circularvection).

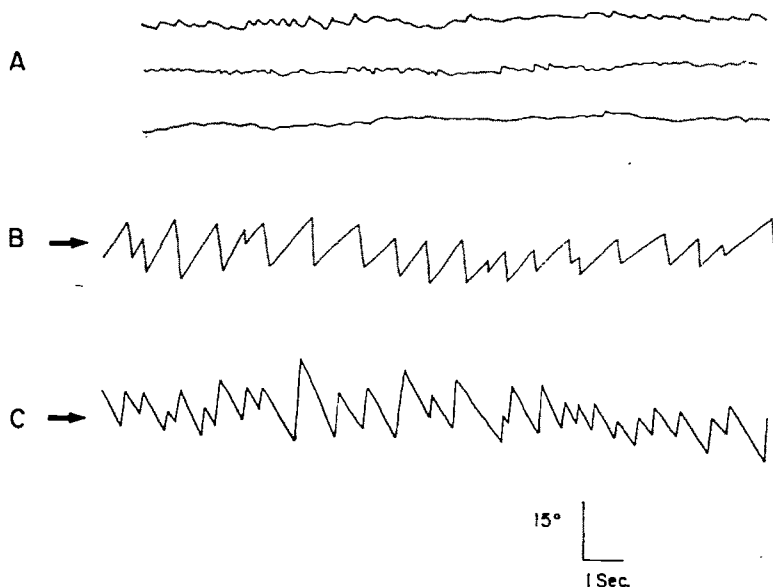
Results

OKN PATTERNS

Several patterns of OKN were observed.

Normal. The normal pattern of OKN was a jerk nystagmus with the slow component in the direction of drum rotation and the fast component in the opposite direction (Fig. 1). The velocity of the slow component was constant during the nystagmus cycle, resulting in a ramp-like shape of the slow component. Eleven patients with motor-defect nystagmus (39%) and 7 patients with sensory-defect nystagmus (39%) displayed this normal OKN pattern during stimulation at the several drum velocities. During optokinetic stimulation the eyes of normal subjects and most patients with congenital nystagmus deviate in the orbit in the direction of

Fig. 1 Normal pattern of OKN. A. Nystagmus during attempted fixation of a stationary target. Top— 10° to right. Centre—primary position. Bottom— 10° to left. Note null position at 10° to left. B. Drum rotating at $60^\circ/\text{s}$ to right. Note ramp-like shape of slow components. Arrow indicates centre position. C. Drum rotating at $60^\circ/\text{s}$ to left. Arrow indicates centre position. Deflections up are to the right, deflections down are to the left.

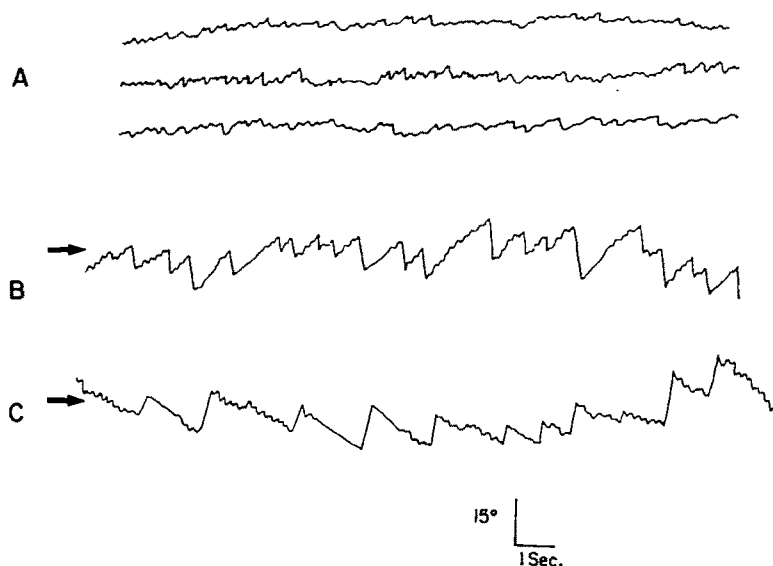


the fast component of OKN, as shown in Fig. 1. The eyes usually do not deviate more than 15 degrees from the midline. The normal pattern of OKN in patients with congenital nystagmus was not produced by eccentric gaze, as could be seen by comparing nystagmus in eccentric gaze to OKN. In Fig. 1 the null position, or position in which the nystagmus was least in amplitude, was approximately 10 degrees to the left. In most patients the nystagmus has a pendular waveform at the null position and a jerk-like waveform in eccentric gaze to either side of the null position. The fast component

or saccade in eccentric gaze is usually in the direction of eccentric gaze. The relatively large amplitude, ramp-like slow component of the normal pattern of OKN cannot be explained simply as a result of eccentric gaze.

Superimposition. The superimposition pattern of OKN consisted of a high frequency pendular oscillation superimposed on the ramp-like slow component. The slow component was in the direction of drum rotation. A large amplitude fast component was present in the opposite direction (Fig. 2). In several patients with this OKN pattern the high

Fig. 2 Superimposition pattern of OKN. A. Nystagmus during attempted fixation of a stationary target. Top— 15° to right. Centre—primary position. Bottom— 10° to left. Note small amplitude, 5 Hz pendular oscillations. B. Drum rotating at $60^\circ/\text{s}$ to right. Note ramp-like slow component of OKN during intervals in which pendular oscillations are absent. Arrow indicates centre position. C. Drum rotating at $60^\circ/\text{s}$ to left. Arrow indicates centre position. Deflections up are to the right, deflections down are to the left.



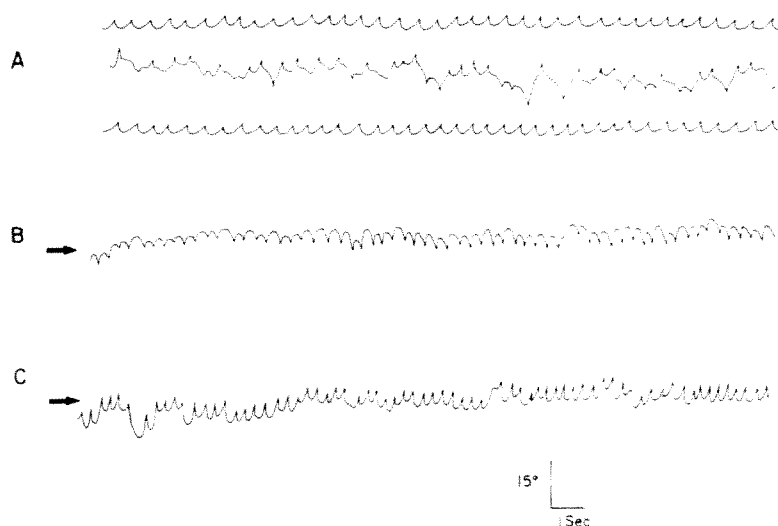


Fig. 3 Pseudoinverted pattern of OKN. A. Nystagmus during attempted fixation of a stationary target. Top— 15° to right. Centre—primary position. Note alteration of cycles with refoveating saccades to right and left, and exponentially increasing velocity of smooth eye movements. B. Drum rotating at $30^\circ/\text{s}$ to right. Note small amplitude saccades to right and smooth eye movements with exponentially increasing velocity to left. Arrow indicates centre position. C. Drum rotating at $30^\circ/\text{s}$ to left. Arrow indicates centre position. Deflections up are to the right, deflections down are to the left.

frequency oscillation was absent during part of the slow component ramp, as illustrated in Fig. 2, showing that the pendular oscillation was in fact engrafted on a smooth optokinetic response. The velocity of the slow component ramp was measured during these intervals of absent pendular oscillation. Four patients with motor-defect nystagmus (14%) and 3 patients with sensory-defect nystagmus (17%) had this OKN pattern.

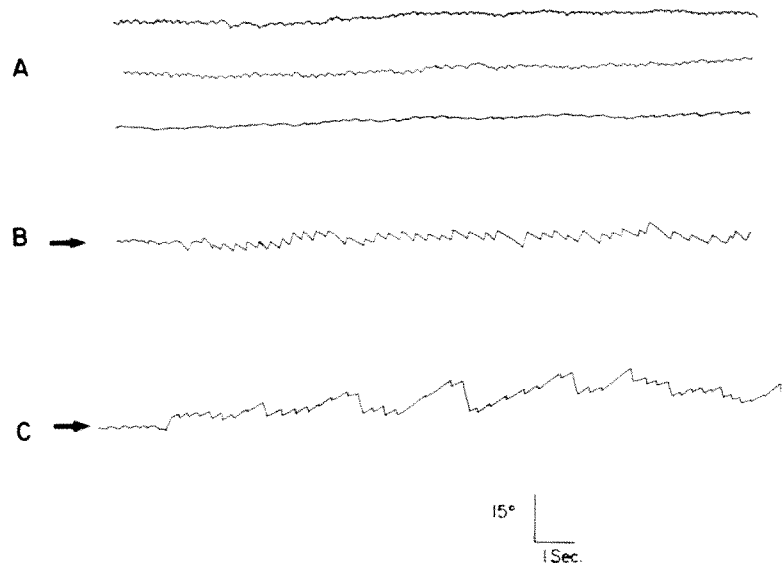
Pseudoinversion and true inversion. The pseudoinverted pattern of OKN consisted of slow components in the direction opposite to drum rotation and fast components in the same direction as drum rotation. This pattern simply represented persistence of the patient's basic nystagmus, that is, the nystagmus pattern during attempted fixation of a stationary target, during optokinetic stimulation rather than true inversion of the optokinetic response. For example, if the saccade in the basic nystagmus waveform was towards the left, during drum rotation to the right there might be little effect on the basic nystagmus, but the saccade towards the left would give the impression that the optokinetic response was in the expected direction. During drum rotation to the left the basic nystagmus would persist, but the saccade toward the left would give the impression that the OKN was inverted. The clinically observed 'inversion' would be present in only 1 direction of drum rotation. Two patients with sensory-defect nystagmus (22%) had this pattern. No patient with motor-defect nystagmus had this pattern.

Some patients showed pseudoinversion of OKN in both directions of drum rotation. In this pattern the saccade of the basic nystagmus waveform was

used to track stripe movement at the lower drum velocities of 10 and 30 degrees/s. In Fig. 3 the basic nystagmus consisted of alternating nystagmus cycles with small saccades to the right and left. Dell'Osso and Daroff¹ have shown that the saccade in each cycle attempts to refoveate the target. During drum rotation to the right the nystagmus cycle with the saccade to the right predominated. During rotation to the left the cycle with the saccade to the left predominated. However, close examination of the recorded eye movements showed that OKN was not actually inverted. The smooth eye movements of the nystagmus pattern during drum rotation in both directions had exponentially increasing velocities rather than the constant velocities of the ramp-like slow components of the normal OKN pattern. These smooth movements represent the smooth movements of the basic nystagmus waveform and not inverted slow components of OKN. As shown in Fig. 3, this pattern of 'pseudoinversion' of OKN was not produced by the effect of eccentric gaze on the basic nystagmus. Three patients with motor-defect nystagmus (11%) and 2 patients with sensory-defect nystagmus (11%) had this pattern.

True inversion of OKN with reversal of ramp-like slow components was found in only 2 patients with motor-defect nystagmus (7%) and in 2 patients with sensory-defect nystagmus (11%), 1 patient with ocular albinism, and 1 patient with oculocutaneous albinism. In Fig. 4 the slow components of OKN were ramp-like with constant velocity. A gradual build-up of reversal during constant velocity drum rotation was occasionally observed. Therefore most instances of 'inversion' of OKN detected by clinical

Fig. 4 *Inverted pattern of OKN. A. Nystagmus during attempted fixation of a stationary target. Top—15° to right. Centre—primary position. Bottom—15° to left. Note null position at 15° to left. B. Drum rotating at 30°/s to right. Note slow components are ramp-like and to the left. Arrow indicates centre position. C. Drum rotating at 30°/s to left. Note slow components are to the right. There is gradual build-up of slow component velocity. Arrow indicates centre position. Deflections up are to the right, deflections down are to the left.*



observation alone were found to represent pseudo-inversion rather than true inversion when examined by eye movement recordings.

OPTOKINETIC GAIN

Gain was not measured in patients with the pseudo-inverted or true inverted pattern of OKN. Twenty-three patients with motor-defect nystagmus (82%) had optokinetic responses in which the OKN gain could be measured; whereas only 10 patients with sensory-defect nystagmus (56%) had measurable OKN gains. The gains from constant velocity tests and sinusoidal tests are presented in Table 1. The data from constant velocity drum rotation to the right are presented. Data from leftward drum rotation were similar. The OKN gain in motor-defect nystagmus was greater than that in sensory-defect nystagmus. For example, during constant velocity drum rotation at 30°/s the mean OKN gain ± 1 SD for patients with motor-defect nystagmus was 0.38 ± 0.19 , whereas the gain in patients with sensory-defect nystagmus was 0.22 ± 0.19 . The

mean OKN gains for both groups were significantly different from that of normal subjects in our laboratory, 0.81 ± 0.09 .¹¹ The gain in patients with motor-defect nystagmus was significantly greater than that in patients with sensory-defect nystagmus ($P < 0.01$, Student's *t* test). The difference between the patient groups at 60°/s was significant at the 1% level, but the difference at 10°/s was not significant at the 5% level. During sinusoidal drum rotation (0.05 Hz, 30°/s), the mean gains in both patient groups were significantly lower than in normal subjects ($P < 0.01$, Student's *t* test), and were significantly different from each other ($P < 0.02$, Student's *t* test). The mean gain in motor-defect nystagmus was 0.39 ± 0.14 , and in sensory-defect nystagmus was 0.16 ± 0.18 . The mean gain in normal subjects in our laboratory was 0.75 ± 0.15 . The difference between the patient groups at 60°/s was not significant at the 5% level.

The hypothesis that OKN gain was linearly related to visual acuity was evaluated in all patients and within each patient group. However, linear

Table 1 *Optokinetic gain*¹

	Constant drum velocity ²			Peak sinusoidal drum velocity ³	
	10°/s	30°/s	60°/s	30°/s	60°/s
Normal subjects	0.88 ± 0.07^4	0.81 ± 0.09	0.79 ± 0.13	0.75 ± 0.15	0.71 ± 0.22
Motor-defect nystagmus	0.29 ± 0.13	0.38 ± 0.19	0.35 ± 0.18	0.39 ± 0.14	0.25 ± 0.17
Sensory-defect nystagmus	0.20 ± 0.17	0.22 ± 0.19	0.19 ± 0.19	0.16 ± 0.18	0.18 ± 0.12

¹Gain = peak eye velocity/peak drum velocity. ²Constant drum rotation to the right. ³Sinusoidal drum rotation at 0.05 Hz. ⁴Mean gain ± 1 SD.

regression analysis indicated that correlation coefficients of OKN gain and visual acuity were not statistically significant among all patients (0.577, $P > 0.05$), within the motor-defect group (0.524, $P > 0.05$) or within the sensory-defect group (0.299, $P > 0.05$).

OKAN AND CIRCULARVECTION

None of the 32 patients tested had OKAN after constant velocity optokinetic stimulation in either direction. Some patients had persistence of their basic nystagmus with eyes opened in the dark with or without previous optokinetic stimulation. This nystagmus was not interpreted as representing OKAN. Eighteen patients with motor-defect nystagmus (64%) and 7 patients with sensory-defect nystagmus (40%) experienced circularvection (CV). Characteristically, the patients reported an illusion of self-rotation in the direction opposite to that of drum rotation beginning 5 to 10 seconds after onset of optokinetic stimulation. CV ended abruptly when stimulation was terminated by turning off the lights. No correlation between OKN gain and CV was found in either patient group.

Discussion

Convincing evidence has been presented that OKN results from simultaneous stimulation of a subcortical optokinetic system and the pursuit system in many species. Ter Braak^{12,13} showed that afoveate animals, such as the rabbit, produced OKN in response to movement of large objects (passive OKN) but did not track small objects of possible 'interest' to the animal. Passive OKN persisted after removal of the cerebral hemispheres in these animals and was presumably produced by an entirely subcortical ocular motor system. Animals with a fovea or area centralis, such as the monkey and dog, had both passive and active OKN. Only active OKN was lost after removal of the cerebral hemispheres or occipital lobes, and presumably utilised cortical pathways.

Recent studies of OKN in human patients with localised lesions affecting the ocular motor system¹⁴⁻¹⁶ suggest that the optokinetic response in man consists of contributions from the smooth pursuit system and a subcortical optokinetic system. The smooth pursuit contribution depends on stimulation of the fovea, utilises the retino-geniculocalcarine sensory pathway and the occipito-mesencephalic motor pathway, and produces the rapid build-up of slow component velocity of OKN observed after a step of optokinetic stimulation. The contribution from the subcortical system is similar to OKN in afoveate animals, such as the

rabbit.¹⁷ This contribution depends on stimulation of motion-sensitive cells in the retina¹⁸⁻²⁰ that project via the accessory optic tract to cells in the nucleus of the optic tract.²¹ There is convincing evidence that motion-sensitive retinal ganglion cells are the input stage of the optokinetic loop in the rabbit, since their firing rates have been shown to correlate with the velocity of OKN.²² Cells in the nucleus of the optic tract in turn project to the vestibular nuclei and cerebellum.²³ The optokinetic response in afoveate animals is characterised by a slow, gradual build-up of slow component velocity over many seconds and OKAN. In several patients with localised lesions of the parietal lobe¹⁶ and cerebellar flocculi¹⁶ whom we have reported on OKN was characterised by a slow build-up of slow component velocity and preservation of OKAN. Smooth pursuit was severely impaired such that the subcortical contribution to OKN was 'uncovered'. Ter Braak¹⁴ described a man who was cortically blind from histopathologically verified infarction of the occipital lobes, who had no pursuit, but who showed the persistence of OKN with a slow build-up and OKAN with rotation of a surrounding optokinetic drum in one direction. Presumably the OKN in this patient was produced by the subcortical optokinetic system.

The pursuit system is probably abnormal in congenital nystagmus. The function of this system is difficult to measure, since the smooth movement velocities of the spontaneous nystagmus are very high (up to 90°/s) and a relatively small velocity contribution from pursuit is difficult to detect. Pursuit function has been measured in a few patients with relatively low velocities and has been shown to be subnormal.^{2,24}

In normal human subjects OKAN (present in approximately 70% of subjects in our laboratory) circularvection and postcircularvection in the dark probably result from stimulation of the subcortical system.⁸⁻¹⁰ In our patients with congenital nystagmus slow build-up of OKN, OKAN, and post circularvection were not observed. In most patients nystagmus was greatly reduced in amplitude or absent in the dark with loss of fixation. We would expect that OKAN could be easily observed if it were present. Although the slow component of OKN could be obscured by the high velocity smooth movements of the basic nystagmus in the light, the low-velocity slow component of OKAN should be detectable in the dark. The absence of OKAN in our patients was another indication that a normal optokinetic response was not simply hidden by the intense basic nystagmus. Most of our patients did experience circularvection during optokinetic stimulation, however. Circularvection does not appear to

correlate with OKN in congenital nystagmus. A severe defect in the subcortical optokinetic system, therefore, appears to be present. It is unlikely that the impaired OKN in congenital nystagmus can be explained simply by poor visual acuity. Defects of central vision resulting from acquired lesions of the macula in man can be associated with normal OKN.²⁵

The abnormalities of OKN in patients with motor-defect nystagmus were qualitatively similar to but quantitatively different from those in patients with sensory-defect nystagmus. This suggests that the type and location of defect(s) are similar in both groups but that the severity is variable. In motor-defect nystagmus we might hypothesise that developmental anomalies are present in the pursuit and subcortical optokinetic systems at birth. A degree of postnatal development might be required in these systems. In sensory-defect nystagmus the absence of well-formed retinal images or normal conduction through the optic nerves due to bilateral opacities of the ocular media or bilateral optic atrophy could interrupt this postnatal development. Alternatively, in sensory-defect nystagmus 2 distinct, unrelated defects in the visual afferent and ocular motor systems may be present. The ocular motor lesion would be identical to that in motor-defect nystagmus. Although no basic differences have been found between motor-defect nystagmus and sensory-defect nystagmus in nystagmus waveform, frequency, and amplitude,² or in patterns of OKN, this classification of congenital nystagmus is still clinically useful. It emphasises the need to search carefully for associated ocular lesions. The presence of lesions has important implications for the prognosis for useful visual function and evaluating clinical indications for prism and surgical therapies. We have found that measurement of the patient's best visual acuity in the null position and/or with convergence in which the nystagmus amplitude is minimised is helpful in indicating that associated ocular lesions are present. Visual acuity is usually less than 20/80 in sensory-defect nystagmus and better than 20/60 in motor-defect nystagmus despite similar amplitude of nystagmus. Careful clinical ophthalmic examination, including measurement of visual acuity in the null position and tests of colour vision, is still the best means of detecting associated ocular lesions.

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Contraction anisocoria: nasal versus temporal illumination

SHIRLEY A. SMITH AND S. E. SMITH

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SUMMARY The size of the pupillary reflex responses to flashes of light from 2 sources, positioned on each side of the visual axis, was measured in both eyes of 20 healthy subjects. When the nasal retina of one eye was illuminated, the direct reaction of that eye exceeded the consensual reaction of the other eye by a mean of 6.1% of reflex amplitude, whereas illumination of the temporal retina gave equal reflex responses.

Earlier work established that when one eye alone was stimulated with a flash of light the pupillary reflex amplitude in that eye exceeded the consensual reaction of the other eye.¹ Although the magnitude of this contraction anisocoria was small (mean value 0.075 mm or 6.1% of reflex amplitude) it was found commonly in normal subjects, in contrast to the findings of other authors.^{2,3} The position of the light source used by Smith *et al.*¹ was such that only the nasal retina was illuminated, whereas other workers used larger centrally placed light sources giving general retinal illumination. The present study was designed to test whether stimulation of the temporal retina results in the same degree of contraction anisocoria.

Materials and methods

Twenty healthy subjects of both sexes, mean age 28 years (range 19-49 years), who had no history of eye disease volunteered for the study. Vertical pupillary diameters were measured with a binocular infrared sensitive television pupillometer as described previously.¹

Light reflexes were elicited by light flashes of 500 ms duration from 2 light sources (Sylvania 2 W tungsten arc lamps) positioned on either side of the visual axis of one eye and in the same horizontal plane. Both conical light beams were focused to a diameter of 1.8 mm in the plane of the pupil. One formed a mean angle of incidence of 6°30' to the visual axis to illuminate the nasal retina 2°20' to 10°40' from the macula, that is, most of the area

Table 1 Mean contraction anisocoria in 40 eyes on nasal versus temporal retinal stimulation

Retinal stimulation	Direct minus consensual reflex amplitude (mm)			Percentage of averaged reflex amplitude		
	Mean	SEM	P	Mean	SEM	P
Nasal	0.08	0.02	<0.001	6.1	1.5	<0.001
Nasal + temporal	0.04	0.02	<0.05	2.5	1.1	<0.05
Temporal	0.02	0.02	NS	1.6	1.1	NS

NS = not significant.

between the macula and the blind spot. The other formed a mean angle of 14°30' to the visual axis to illuminate the temporal retina 10°20' to 18°40' from the macula. The light intensities of each source were individually attenuated with Wratten neutral density filters to give submaximal and approximately equal pupillary reflex responses within the range 1.0 to 2.0 mm.

Flashes of light from either or both sources were directed at one eye every 8 s to give the following sequence of retinal stimulation: nasal and temporal together, nasal, then temporal. After one eye had received this sequence 3 times the experiment was repeated on the other eye. The resulting triplicate measurements of reflex amplitude for each of the 3 types of retinal stimulation were averaged.

Results

The occurrence of contraction anisocoria was found to depend on the position of the light upon the retina (Table 1). The difference between the direct and consensual reflex amplitude was greatest when the nasal retina alone was stimulated. The mean

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contraction anisocoria was 6.1% of mean reflex amplitude on nasal stimulation and 2.5% when both lights were on together. The direct and consensual reflexes did not differ significantly when the temporal retina alone was illuminated.

Discussion

These results confirm that a small degree of contraction anisocoria results from flash illumination of the nasal retina of one eye. When the light source was on the other side of the visual axis to illuminate the temporal retina the light reflexes were of equal size. Stimulation of the nasal retina thus appears to provide a stronger stimulus to the pupil of the same eye than it does to that of the contralateral eye, though the difference is small (6.1% of mean reflex amplitude).

The optic nerve fibres arising from the nasal retina cross in the chiasm and according to Kupfer

*et al.*⁴ the number of crossed fibres in the optic tract in man exceeds the number uncrossed by 6%. However, for contraction anisocoria to have an anatomical basis it is necessary to postulate asymmetry in the subsequent decussation of fibres subserving pupillary function which occurs in the midbrain. There is no evidence for such an asymmetry, and at present no explanation can be offered for these results.

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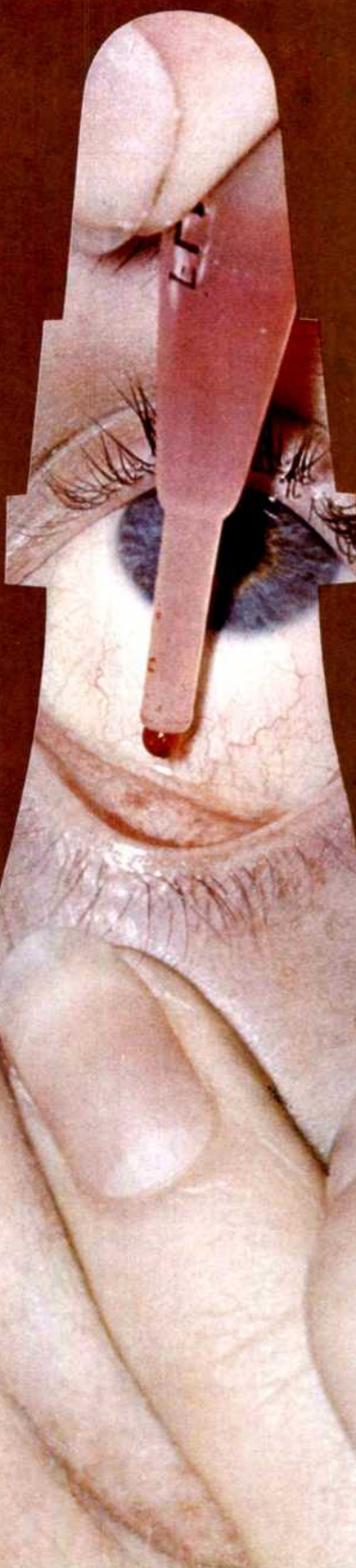
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Oncocytomas (oxyphil adenomas) of the lacrimal caruncle

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SUMMARY Three cases of oncocytoma (oxyphil adenoma) of the lacrimal caruncle are reported. Transmission electron microscopy performed on one of the lesions confirms the tumour to be composed of cells containing abnormally large numbers of mitochondria. It is suggested that these tumours arise from accessory lacrimal glands or their secretory ducts.

Oncocytomas arising from the lacrimal caruncle are extremely uncommon tumours. It is generally accepted that Radnot's report¹ was the first. She described an 'oncolytic cyst' which had been removed from the caruncle of a 69-year-old male. Since that report probably only 25 oncocytic lesions of the caruncle have been reported. These lesions have masqueraded under a variety of names, adding to the confusion which surrounds this lesion. They have been described as oncocytomas,²⁻⁷ oxyphil adenomas,^{8,9} papillary cystadenomas,¹⁰⁻¹² adenolymphoma-like tumours,¹³ and Warthin's tumour.¹⁴ The author here reports 3 cases of caruncular oncocytoma and in addition comments on the transmission electron microscopic appearances and histogenesis of this curious lesion.

Case reports

CASE 1

The patient, a 73-year-old female, initially presented to the ophthalmic department in April 1975. She complained of reduced vision and pain in her right eye. On examination she was found to have a dendritic ulcer with secondary anterior uveitis; this was successfully treated with idoxuridine and atropine. In June 1977 she returned to the ophthalmic clinic complaining of photophobia and soreness of her eyes. She was found to have keratoconjunctivitis sicca, with positive staining of the cornea by rose Bengal, and a Schirmer's test showing reduced tear secretion (right eye 5 mm, left eye 3 mm in 5 min); she was treated with guttae methylcellulose.

In August 1977 she returned to the clinic for a routine follow-up visit. At this examination a swelling arising from the right lacrimal caruncle with numerous engorged blood vessels passing

over its surface was noted. On questioning, the patient disclosed that she had noted a small swelling of the inner part of her eye for the past 3 or 4 years. The lesion was excised and submitted for histology.

Histological examination

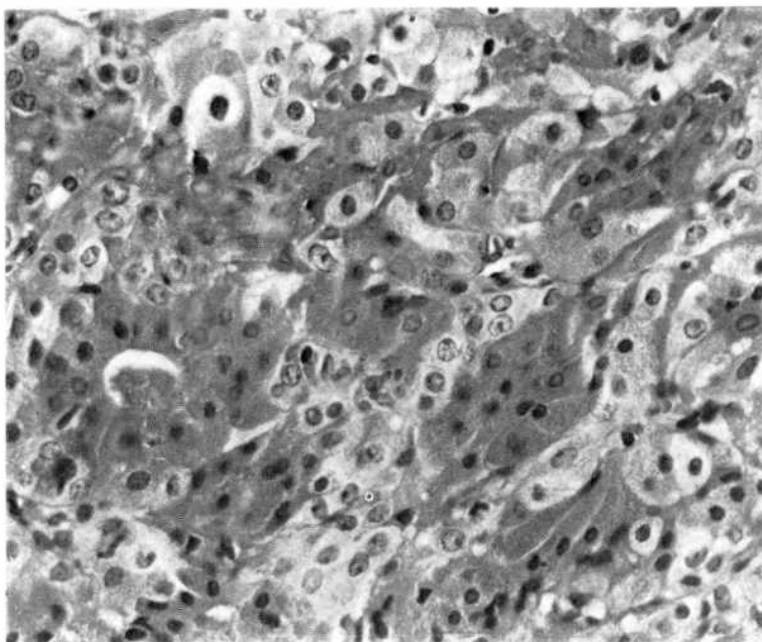
Macroscopic appearance. The specimen consisted of a nodule of brown tissue 5 mm in diameter.

Microscopical appearance. The tumour was composed of large polygonal, granular, eosinophilic cells. Two cell types were clearly discernible (Fig. 1). The first cell type had an intensely eosinophilic, homogeneous cytoplasm. These cells had a sharply angular configuration, with indistinct cell borders. The appearance suggested that they had been compressed by the second cell type present. The nuclei of this cell type were predominantly large, round or oval, with a prominent nucleolus. Occasional large 'atypical' nuclei were also present. Moreover, a few cells appeared binucleate. No mitotic figures were noted in the sections studied.

The configuration of this tumour was of a solid sheet of cells. However, occasional simple glandular structures were present, particularly at the periphery of the tumour. The tumour was encapsulated by a thin condensation of connective tissue.

Electron microscopy. Examination of the tumour by transmission electron microscopy confirmed the presence of large numbers of mitochondria within the cells. The distinction between light and dark cells appeared to be entirely due to the concentration of mitochondria within the cytoplasm. The mitochondria were morphologically abnormal, showing great variation in shape and size. Morphologically some of them were round or oval, while others were grossly elongated or fusiform in nature. Many contained densely packed longitudinal orientated cristae. This arrangement is identical to the para-

Fig. 1 Case 1. A 'solid' oncocytoma showing distinct light and dark cells. Simple acinus formation is seen at the left hand edge of the section. (H & E, $\times 160$).



crystalloid bodies described in a caruncular oncocytoma described by Radnot and Lapis.⁵ Occasional desmosomes were noted between the tumour cells. Unfortunately, poor fixation precluded a more detailed examination by electron microscopy.

CASE 2

The patient, a 51-year-old female, presented at the ophthalmic clinic in February 1977 with a 20-year history of epiphora of the right eye. She stated that her tear duct had been 'pierced' many years previously. On examination the right nasolacrimal duct was found to be obstructed. In addition a papilliferous growth was present, arising from the right lacrimal caruncle. The lesion was excised and submitted for histological examination.

Histological examination

Macroscopic examination. Macroscopically the specimen consisted of a nodule of tissue measuring 4 mm in diameter.

Microscopic examination. Histologically the tumour consisted of epithelial cells arranged in a tubular papillary configuration (Fig. 2). In some areas the tubules formed large cystic spaces. In other areas the tubular configuration was not apparent, the cells forming a more solid structure. The tubules were lined by tall columnar, granular, eosinophilic cells. The nuclei were situated subterminally. Between the bases of the columnar cells smaller, rather indistinct, polygonal cells were

present. These cells were similarly eosinophilic. The tubules were separated by a delicate stroma which contained capillaries. The nuclei showed little pleomorphism. Mitotic figures were not observed in the sections studied. Occasional mucus-secreting goblet cells were present in the epithelium; these cells stained strongly by the alcian blue method. The cystic spaces contained amorphous material which stained positively with the periodic acid Schiff and alcian blue methods.

The tumour was surrounded with a thin delicate capsule. In one section studied the epithelium of the tumour appeared in close apposition to the caruncular epithelium. The surrounding stroma of the caruncle contained hair follicles, sebaceous glands, and 2 accessory lacrimal glands. One of the glands contained simple secretory ducts. The epithelium of the ducts was composed of large granular eosinophilic cells similar to those in the tumour (Fig. 3). This presumably represented oncocytic metaplasia of the ductal epithelium. No communication between the gland and the metaplastic secretory ducts could be demonstrated.

CASE 3

The patient, a 74-year-old female, presented to the Ophthalmic Clinic in November 1964 with a history of gradual visual loss. Her visual acuity at that time was right eye 6/36, left eye 6/24. This was corrected to 6/18 both eyes with a -1.5 dioptre sphere. On examination bilateral immature lens opacities were

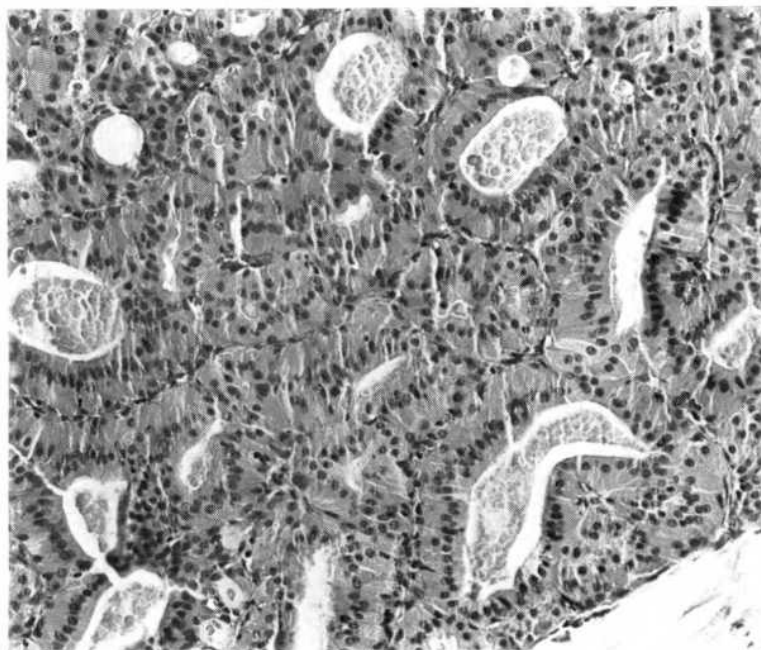


Fig. 2 Case 2. An oncocytoma with a pronounced papillary cystic configuration. Note the back to back formation of the oncocytes separated by a delicate stroma. (H & E, $\times 60$).

found. In addition a small cystic lesion of the right caruncle was noted. The patient stated that this lesion had been present for several years and was not causing any discomfort.

In October 1967 she attended the Ophthalmic Clinic again. Her visual acuity was now right eye 6/36, left eye 5/60; this was not corrected with lenses. The caruncular lesion was still present and was apparently unchanged in size. In April 1968 bilateral intracapsular lens extractions were per-

formed. Postoperatively her corrected visual acuity was 6/9 in both eyes. In December 1971 the patient attended the Ophthalmology Clinic again because the lesion of her right caruncle was increasing in size and now troubling her. The lesion was described as being a cystic swelling with several large blood vessels crossing its anterior surface. These appearances led to the tentative diagnosis of an angioma. The lesion was excised and submitted for histological examination.

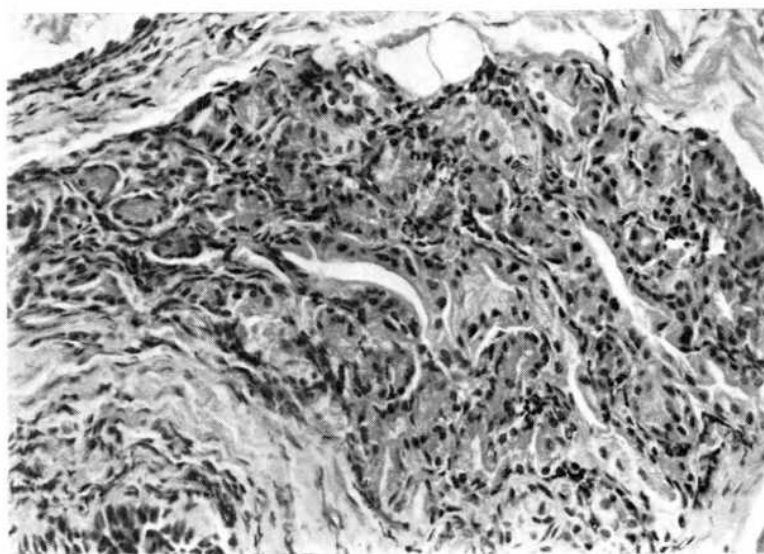


Fig. 3 Case 2. An accessory lacrimal gland containing a secretory duct exhibiting marked oncocytic metaplasia, slightly right of centre. (H & E, $\times 105$).

Pathological examination

Macroscopic appearances. The lesion was described as a ruptured cyst measuring 5 mm in diameter.

Microscopic examination. Histologically the cyst wall was composed of granular, intensely eosinophilic cuboidal cells forming a papillary-tubular structure. Occasional cells contained large brownish granules in their cytoplasm. These granules did not stain by any silver impregnation technique and were considered to be lipofuscin granules. Scanty mucus-secreting cells were present throughout the lesion. There was little nuclear pleomorphism, and mitotic figures were not identified in the sections studied. A scanty condensation of connective tissue surrounded the lesion.

Discussion

The term oncocyte was devised by Hamperl¹⁸ to describe an epithelial cell that was characterised by its large size and eosinophilic granular cytoplasm. The derivation of the term (Greek: Onkausthai—to swell) was thought by Hamperl to convey the essential morphological characteristic of the cell, namely its large swollen appearance. Electron microscopic studies^{16–18} (and case 1 of this report) have since shown that the essential feature of these cells is the number of mitochondria within the cytoplasm. It is believed that the increase in mitochondria in the oncocyte reflects a defect of metabolism in this organelle leading to a compensatory increase in their number.¹⁹ Though the primary metabolic defect is not known, it is thought to arise in old 'burnt out' cells, a concept inferred from the increasing incidence on oncocytic lesions with age.

Benign oncocytomas arising in ocular adnexa have been described in the lacrimal gland, lacrimal sac, plica semilunaris, bulbar conjunctiva, upper and lower fornices, mucocutaneous junction, and lacrimal caruncle. Of these, the caruncular oncocytoma is by far the commonest; however, even in this site it is a rarity. In a study of 200 lesions arising from the caruncle Evans²⁰ described only 1 case which may have been an oncocytoma, the precise histological details being unavailable. Since that report probably only 25 cases (excluding this report) have been described.

Oncocytomas are generally regarded as benign tumours. However, sporadic reports of malignant oncocytomas have appeared. Malignant oncocytomas of the parotid have been described.^{21–23} One case arising from a gland in the nasal mucosa has also been described.¹⁹ Four malignant oncocytomas arising in ocular adnexa have been described, 2 arising in the lacrimal sac^{24,25} and 2 occurring in the lacrimal gland.²⁶ In relation to the lacrimal gland

only 1 benign oncocytoma has been described.²⁷ It is surprising that so few lacrimal oncocytomas (benign or malignant) have been described, especially when one considers the fact that oncocytic metaplasia is known to occur in this organ. Bock and Schlagenhauff²⁸ examined the lacrimal glands of 20 necropsies and found oncocytic metaplasia in 7 of them (35%). Equally surprising is the apparent excess of malignant tumours to benign lesions. It is possible to attribute these anomalies to the extremely slow growth of the benign oncocytoma.

Case 3 above illustrates the extremely slow growth of this tumour. The lesion was present for at least 7 years before excision. Thus benign lacrimal oncocytomas may never attain sufficient size to cause symptoms and thus escape detection. In contrast, a malignant lesion with its more rapid growth and invasion of adjacent tissues would be expected to produce symptoms.

HISTOGENESIS OF CARUNCULAR ONCOCYTOMAS

The histogenesis of the caruncular oncocytoma is still open to discussion. Anatomically the lacrimal caruncle is a piece of modified skin. It is covered by stratified squamous epithelium and contains hair follicles, sebaceous glands, and sweat glands. It differs from skin in that it contains accessory lacrimal glands similar to those of Krause.

These glands are usually in the centre of the caruncle and open by a sinuous duct near the plica semilunaris.²⁹ Three possible sites of origin are proposed—the surface epithelium, the conjunctiva, and the accessory lacrimal glands. Other suggested sites of origin such as sweat glands³ or mucous glands¹³ seem improbable, for oncocytomas are not described arising from these structures in other sites.

The accessory lacrimal glands or ducts have been proposed as the site of origin by several authors^{1,2,5,6,10–12} in view of their histological appearances (see below). Greer³ described 2 cases of caruncular oncocytoma which appeared to arise from the surface epithelium. Case 2 above similarly showed close apposition to the surface epithelium. However, in this example oncocytic metaplasia was present in the duct of an accessory lacrimal gland present near the tumour, though a direct continuation between the 2 could not be demonstrated. Forbes and Crawford¹¹ described a case in which a dilated secretory duct displaying oncocytic metaplasia was in direct continuity with an oncocytoma. A possible explanation for the existence of a lesion in apparent continuity with the surface epithelium as described by Greer³ and the author (case 2) is that the lesion could have arisen from the epithelium

of a secretory duct immediately beneath the caruncular epithelium. Briggs and Font⁶ described focal oncocytic metaplasia in the ducts and acini of accessory lacrimal glands present in the region of the caruncle. Radnot and Lapis⁵ examined an oncocytoma with the transmission electron microscope and found, particularly at the periphery of the lesion, epithelial cells morphologically identical to those of accessory lacrimal glands. It would seem unlikely that oncocytomas arise from the caruncular epithelium proper, as this is a stratified squamous epithelium similar to skin, and, so far as the author is aware, oncocytomas have not been described arising from cutaneous structures elsewhere in the body.

It is possible that caruncular oncocytomas arise from the conjunctiva immediately adjacent to the caruncle. In support of this argument Briggs and Font⁶ described 2 oncocytomas apparently arising from the bulbar conjunctiva near the plica semilunaris. If oncocytomas were to arise mainly from the conjunctiva, then one should anticipate oncocytic changes described more frequently in the conjunctival epithelium, but this is not the case. Moreover, in relation to lesions described arising from the plica semilunaris, it is to be noted that this is the site of drainage of the secretory duct of the caruncular lacrimal tissue. It would appear that the majority, if not all, caruncular oncocytomas arise from accessory lacrimal glands or their secretory ducts. This belief is supported by the similar histological appearances of oncocytomas occurring at the caruncle and those occurring in other secretory glands, namely the major salivary glands.

CLINICAL ASPECTS

To the clinician the caruncular oncocytoma is a rarity. Nevertheless the diagnosis should be considered when he sees a caruncular swelling, particularly if the lesion appears cystic or has a bright cherry red colour. The lesion appears to occur mainly in postmenopausal females. In the 28 cases recorded, including this report, 5 patients have been male (in one case the sex of the patient was not given), a ratio of 5.6:1 females to males. It usually has an extremely slow rate of growth and often presents as a chance finding.

The author thanks Miss M. A. C. Jones and Mr C. A. L. Palmer for allowing the publication of their clinical material; Professor L. Henry and Mr A. Stanworth for their help and encouragement; Miss F. Bishop and Mrs S. Porter for their assistance with the technical preparation of the specimens.

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A new lid clamp (Fig. 1) has been devised mainly for the upper lid—though it may also be used for the lower lid—to facilitate surgery when the total area of the lid has to be exposed. It will thus have a use in such procedures as entropion correction involving grey-line splitting with or without grafting (mucous membrane or skin), excision of tumours when partial or total resection of lid becomes necessary followed by plastic reconstruction of the lid, and any plastic procedures in which the whole lid must be available for unimpeded manipulations. It may also be used in ptosis surgery by the anterior approach.

The clamp has a subsidiary use as a lip clamp to remove buccal mucous membrane.

The essential advantage of the clamp is that the whole lid (upper or lower) is fully exposed and held in position from the medial to the lateral canthus, both canthii being easily and fully accessible, unobstructed by the instrument. Vertically the lid becomes available to any width desired right up to the orbital margin. The clamp can be fixed at any height on the lid, and the skin of the lid may be stretched and held as needed. Further, the lid margin may be everted and exposed for grey-line surgery. The eversion may even facilitate some procedures from the conjunctival surface for entropion correction. Complete access to the whole lid, including both canthi, is possible because of the lateral arch



of the anterior blade and the absence of a vertical limb at the medial end.

Other functions of the clamp are to provide effective control of bleeding so that a bloodless field is available during surgery, which in turn facilitates a neat and quick procedure. It also gives complete protection of the cornea and the eyeball even when working at the ends of the lid; the posterior plate of the instrument covers the eye ball completely both horizontally and vertically. The posterior plate stretches the lid, facilitating correct procedures. Though the clamp was originally designed for the upper lid, it may well be used for surgery on the lower lid simply by using the right clamp for the left eye and vice versa.

The clamps are designed for right and left lids. There are two versions: large, to be used for large and horizontally long lids; small, for small eyes and in children. Each clamp has anterior and posterior blades which can be tightened to any desirable pressure by the screw on the handle. The anterior blade is sickle-shaped with a curve arching outwards (laterally) to allow easy access to the lateral canthus. The horizontal bar continues parallel with a minimal curve to conform to the superior orbital rim and reaches to the medial end of the lid along the orbital margin. This curve of the horizontal bar allows application of the clamp as far upwards as desired, thus exposing the anterior lid surface maximally. The horizontal bar does not bend down the medial end, so that the instrument does not obstruct the medial part of the lid, and complete access is provided. The posterior blade, which goes under the lid on the conjunctival surface, extends the entire length and breadth of the lid, so that it stretches the lid sufficiently and fixes it to facilitate operative procedures. The blade has a concave posterior surface to align with the cornea and the globe, so that the cornea and the globe are effectively protected during the whole surgical procedure even when the surgeon is working at both ends of the lid.

Correspondence to Dr Tommy.

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References: 1. Romagnoli L, Nagarajaraman S, and Rajagopalan D. Double masked cross-over comparison of Ganda 1+0.2 (Guanethidine 1% and Adrenaline

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Book reviews

Collagenase in Normal and Pathological Connective Tissues. (Ed.) DAVID E. WOOLLEY and JOHN M. EVANSON. Pp. 292. £16.00. John Wiley: Chichester. 1980.

In 1978 a symposium was held in Manchester on the subject of collagenase, and the participants were invited to contribute to a monograph with the object of describing and evaluating progress in this field. The result is a satisfying account of what is known about collagenase as distinct from many published accounts of symposia, which are often tantalisingly inadequately documented and referenced. The editors are to be praised for fashioning a comprehensive text which is clear and reads well even to the non-expert.

Successive chapters provide a brief account of the substrate collagen, reviews of collagenase action release and regulation, and descriptions of the role of collagenase in a variety of tissues. A final chapter tabulates the literature references on vertebrate collagenases up to 1978. Of special interest to those concerned with the eye is an account by Michael Berman of collagenase and corneal ulceration. In conformity with findings in other tissues he reviews evidence that collagenase is formed by the corneal fibroblasts in response to cell-cell interaction with the overlying epithelium. Released as a zymogen or bound to an inhibitor, the enzyme can be activated by plasmin and other proteolytic systems. Corneal epithelium is able to secrete a plasminogen activator which will both promote collagenase activity on the part of the fibroblast-derived enzyme and, through complement, attract polymorphonuclear neutrophil leucocytes, which are also a source of collagenolytic activity. The role of collagenase inhibitors, such as α_2 -macroglobulin, in the cornea is also discussed, as is the role of medroxyprogesterone in controlling collagenase secretion.

This book has much to offer both clinicians and nonclinicians concerned to understand the nature of corneal ulceration and inflammation and, to a lesser extent, of scleritis. The standard of production is good, and there is a useful index.

ALEC GARNER

Computerized Tomography. Vol. 3. No. 4. (Ed.) MELVIN G. ALPER. Pp. 331. \$17.50. Pergamon Press: Oxford. 1979.

This volume of the journal, edited by Dr Melvin G. Alper, from Washington, is largely concerned with CT scanning in orbital diagnosis. It includes 5 papers on orbital scanning, and it is interesting that Lloyd (London) performs plain skull films and axial hypocycloidal tomography prior to CT scanning in the investigation of unilateral proptosis. Grove (Boston) advocates CT scanning in trauma both for the location of foreign bodies and the detection of fractures. Dubois *et al.*

(Pittsburgh) used their orbital slices to monitor needle position for aspiration biopsy of lesions in the orbit, and provide a good example of the biopsy of a malignant glioma of the optic nerve in a 65-year-old man. Finally Citrin (Washington) emphasises the importance of coronal scans in the diagnosis of orbital lesions.

Intracranial disorders affecting the visual pathways are discussed by Citrin and Alper (Washington), and they describe 14 cases with lesions involving the intracranial optic nerve, the chiasm, and the retrochiasmal pathways.

This volume is well produced and provides interesting material for those concerned with orbital or neuro-ophthalmic diagnosis. However, the limitation of size (100 pages) precludes the treatment of the subject in any degree of depth.

M. D. SANDERS

Phacoemulsification and Aspiration of Cataracts. By JARED M. EMERY and JAMES H. LITTLE. Pp. 325. £29.50. C. V. Mosby: St. Louis, Missouri. 1979.

This very beautifully produced volume is part elaborate apologia and part technical manual for a subject which continues to be controversial in ophthalmic surgery. The book is divided into 2 principal sections. The first deals with aspects of the so-called Kelman phacoemulsification procedure, and the second, a short section at the back, is confined to a separate instrument, the phacofragmentor.

The first section is divided into parts in the usual manner for dealing with a surgical topic—principles, instrumentation, indications, techniques, complications, and results. The text is a joint product not only of the 2 main authors but also of a considerable array of well known exponents of this form of surgery, each of whom has been invited to explore his views, results, and various modifications of procedure. The result is rather repetitive, both in the text and in the copious illustrations.

As so often happens, the ardent exponents of a new idea find it difficult to be objective. For instance, a stout claim is made that there is no evidence to suggest that ultrasonic vibrations can harm the corneal endothelial cells, whereas readers will be well aware that such evidence has been well documented in the ophthalmic literature. The authors have made comparisons of their technique with standard intracapsular extraction only and fail to recognise that in recent years excellent techniques have been developed for elective extracapsular extraction which do not require the expensive and sophisticated equipment this book has been designed to promote. This is a pity, as the failure is glaring and important. All the results quoted are without controls and are therefore impossible to evaluate as a comparison with alternative techniques.

The second section on phacofragmentation has been written by the inventor, Girard. The claims for this instrument are indeed impressive, though no figures are quoted in the results obtained over a period of several years. One can only surmise why so apparently valuable a tool has failed to find wider favour.

ARTHUR D. MCG. STEELE

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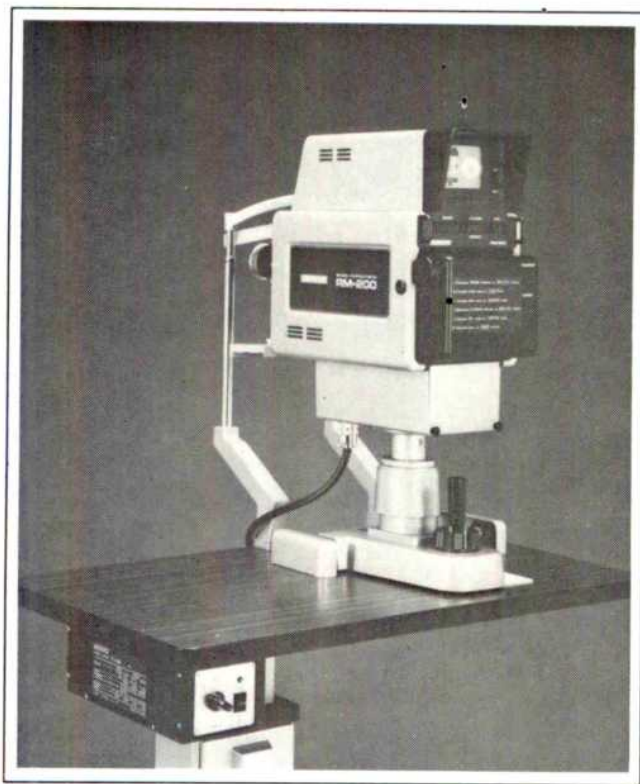


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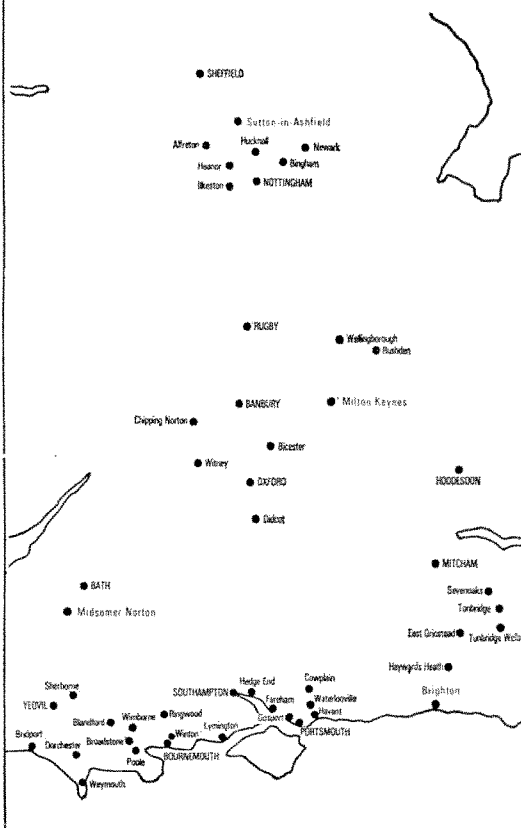
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